No. 2022-1715
(IPR2020-01503)

# United States Court of Appeals
for the
# Federal Circuit

SYSMEX CORPORATION, SYSMEX AMERICA, INC.,

*Appellants*,

v.

BECKMAN COULTER, INC.,

*Appellee*.

APPEAL FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE,
PATENT TRIAL AND APPEAL BOARD IN IPR2020-01503.

**APPELLANTS SYSMEX CORPORATION AND SYSMEX AMERICA, INC.'S CORRECTED OPENING BRIEF**

September 26, 2022

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## ILLUSTRATIVE CLAIM OF U.S. PATENT NO. 10,401,351

7. A sample analyzer comprising:

a plurality of detectors comprising at least one optical detector for optically sensing cells in a sample and at least one electrical detector for electrically sensing cells in the sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring cells in the body fluid sample, and wherein a respective sequence of operations for measuring cells in the blood sample and in the body fluid sample comprises (a) a sensing operation comprising operations of preparing for measurement and operating a detector to sense cells in the sample and (b) an analyzing operation comprising operations of analyzing measurements from the sensing operation and displaying analysis results, and further wherein the plurality of detectors include one or more multi-mode detectors configured to operate in both the blood measuring mode and the body fluid measuring mode,

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise concurrent display of a blood sample option and a body fluid sample option each independently selectable from the other on the input screen and (2) one or more test modes displayed separately from a selected one of the at least two sample-type options;

in response to (I) a user input, on the input screen, of selecting the blood sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting one test mode from the displayed one or more test modes, perform the sensing operation in the blood measuring mode to: prepare a blood measurement sample from the blood sample; introduce at least part of the prepared blood measurement sample into an optical detector; and operate the optical detector to optically sense white blood cells in the

introduced blood measurement sample, and further perform the analyzing operation in the blood measuring mode to: analyze blood-sample measurements of the white blood cells sensed in the introduced blood measurement sample; count each of five types of white blood cells based on the analyzed blood-sample measurements; and display a count of each of the five types of white blood cells; and

in response to (I) a user input, on the input screen, of selecting the body fluid sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting said one or a different test mode from the displayed one or more test modes, perform the sensing operation in the body fluid measuring mode to: prepare a body fluid measurement sample from the body fluid sample; introduce at least part of the prepared body fluid measurement sample into an electrical detector; operate said electrical detector to electrically sense cells in the introduced body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze body fluid-sample measurements of cells sensed in the introduced body fluid measurement sample; count mono-nucleated cells and poly-nucleated cells based on the analyzed body fluid sample measurements; and separately display in a screen a count of the mono-nucleated cells and a count of the poly-nucleated cells.

# CERTIFICATE OF INTEREST

| | |
|---|---|
| **Case No:** | Nos. 2022-1715 |
| **Short Case Caption:** | Sysmex Corporation v. Beckman Coulter Inc. |
| **Filing Party/Entity:** | Sysmex Corporation, Sysmex America, Inc. |

**Instructions:** Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box.** Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: September 26, 2022 Signature: /s/ James R. Sobieraj
Name: James R. Sobieraj

| **1. Represented Entities.** Fed. Cir. R. 47.4(a)(1). | **2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2). | **3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3). |
|---|---|---|
| Provide the full names of all entities represented by undersigned counsel in this case. | Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. | Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. |
| | ☒ None/Not Applicable | ☐ None/Not Applicable |
| Sysmex Corporation | | Japan Trustee Services Bank Ltd. |
| Sysmex America, Inc. | | Sysmex Corporation |

**4. Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

Brinks Gilson & Lione

Andrea L. Shoffstall, formerly with Brinks Gilson & Lione

Daniel A. Parrish, formerly with Crowell & Moring LLP

**5. Related Cases.** Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☒ None/Not Applicable

**6. Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☒ None/Not Applicable

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## STATEMENT OF RELATED CASES

U.S. Patent No. 10,401,351 ("'351 patent") is asserted in the following case pending in the U.S. District Court for the District of Delaware. There have been no appeals from that civil action to this Court. Appellants do not believe that the district court case will be directly affected by the Court's decision in this appeal.

- *Sysmex Corp. et al. v. Beckman Coulter, Inc.*, No. 1:19-cv-1642 (D. Del.).

## JURISDICTIONAL STATEMENT

On February 18, 2022, the Patent Trial and Appeal Board ("Board") issued its final written decision ("FWD") in *inter partes* review ("IPR") No. IPR2020-01503. A1. Sysmex Corporation and Sysmex America, Inc. (collectively, "Sysmex") timely appealed on April 22, 2022. Appx627; 37 C.F.R. § 90.3(a)(1). The U.S. Court of Appeals for the Federal Circuit has jurisdiction over this appeal under 28 U.S.C. § 1295(a)(4)(A) and 35 U.S.C. §§ 141 and 319.

## STATEMENT OF ISSUES

I. Whether the Board's finding that there was an insufficient written description support for a device using an electrical detector to count mono-nucleated cells and poly-nucleated cells in the challenged claims is supported by substantial evidence where:

(a) the '351 specification reasonably conveys to a person of ordinary skill in the art ("POSA") the use of an electrical detector to count the mono- and poly-nucleated cells,

(b) use of an electrical detector to count mono- and poly-nucleated cells was well-known to a POSA at the time of the invention, and

(c) the '351 patent identifies U.S. Patent No. 5,138,181 ("Lefevre") as an alternative embodiment that includes the use of an electrical detector alone to count mono- and poly-nucleated cells.

II. Whether the Board's obviousness decision should be vacated because the Board did not sufficiently explain and support its conclusions that (a) WO 2019/236682 ("Jagtiani") and U.S. Patent No. 8,440,140 ("Nagai") disclose all of the elements recited in the challenged claims and (b) a POSA would have been motivated to combine Jagtiani and Nagai in the way of the challenged claims and reasonably expect success.

## STATEMENT OF THE CASE

## I. TECHNICAL BACKGROUND

### A. Blood Cell Analysis

For many years, blood samples have been analyzed to diagnose various diseases, including anemia, blood cancers, bacterial infections, parasitic infections, and viral infections. Appx2348, ¶ 42. Different types of blood cells that one may detect when analyzing a blood sample include:

- White blood cells ("WBC"): WBCs are also known in the art as "leukocytes[1]," and are part of the body's immune system. Appx1527-1528, ¶ 47. There are five types of WBCs: neutrophils, lymphocytes, monocytes, eosinophils and basophils. *Id.* Monocytes and lymphocytes have a single, round nucleus, and are referred to as "mono-nucleated" cells. Appx1170, [0009]; Appx1543-1544, ¶ 74; Appx2375, ¶ 92. These two cell types also are considered "agranular." Appx1170, [0009]. Neutrophils, eosinophils and basophils consist of cells with multi-nuclear lobes, and are referred to as "polymorphonucleated" or "poly-nucleated" cells. Appx1543-1544, ¶ 74. These three cell types also include a cytoplasm that contains granules, and thus are also called "granular" or "granulocytes." *Id.*

[1] This term is also spelled "leucocytes" in some references. *See, e.g.,* Appx1500, 1:36-56.

- Red blood cells ("RBC"): RBCs are also known in the art as "erythrocytes," and use hemoglobin to carry oxygen throughout the body. Appx1527-1528, ¶ 47.
- Platelet ("PLT"): PLTs are also known as "thrombocytes" and facilitate clotting. *Id.*

When performing a complete blood count, WBCs may be measured as a 5-part differential or a 2-part differential. Appx1171, [0016]. A 5-part differential entails the separation of WBCs into five major classifications (i.e., neutrophils, eosinophils, basophils, lymphocytes, and monocytes) and their quantification on a percent basis. *Id.* A 2-part differential entails the separation of WBCs into two major classifications, i.e., agranular (mono-nucleated) and granular (polynucleated) leukocytes, and their quantification on a percent basis. *Id*.; Appx1543-1544, ¶ 74.

### B. Well-Known Use Of Electrical Detectors For WBC Counts

Prior to the January 31, 2008 filing date of the '351 patent, blood cells were commonly assessed by using either an optical or electrical detector. Appx 1500, 1:13-21; Appx2348-2353, ¶¶ 44-53; Appx2384-2385, ¶ 111. The Board's decision on the written description issue focused on portions of the claims related to an electrical detector. Appx15-26. The preferred embodiment in the '351 specification discloses an electrical detector that uses the well-known Coulter principle to detect

and measure RBCs and WBCs. Appx2385-2386, ¶ 113. The inventor of the Coulter principle described it as follows:

> According to the Coulter principle, when a particle of microscopic size is passed through an electrical field of small dimensions of an order approaching those of the particle, there will be a momentary change in the electric impedance in the ambit of the field. In the thousands of commercial instruments based upon this principle, which have been made available for more than a decade, the change due to the passage of the particle is almost entirely a function of particle size for most all biological and industrial particles.

Appx2349, ¶ 45; Appx2521, 1:67-2:4.

The scientific literature includes a number of publications establishing that a POSA knew that a variety of cells and particles, including WBCs, could be detected for counting using an electrical detector. Appx2349-2353, ¶¶ 46-53; Appx2539-2540; Appx2544; Appx2545; Appx2547; Appx2549; Appx2553; Appx1171, ¶¶ [0018]-[0019]; Appx2557; Appx2563.

The ’351 specification identifies several prior art references that show it was well-known to use an electrical detector to count and classify WBCs into a 2-part differential of mono- and poly-nucleated cells, but not for a 5-part differential. First, the “References Cited” section of the ’351 patent includes U.S. patent application “2003/0030783 Roche et al.” Appx41. The lead named inventor, Mr. Roche, is petitioner’s expert. Appx1504. Roche’s patent application explains the distinction between a 5-part differential and a 2-part differential, and that impedance technology

(*i.e.*, an electrical detector) was able to count white blood cells, but was "unable to provide a five-part differential." Appx1170, [0009]; Appx1141, [0016]; Appx1141, [0018]-[0019]; Appx1173, [0034]; Appx1604, ¶ 18. Consistent with his patent application, Mr. Roche confirmed in his deposition that prior to 2007, a POSA knew that electrical detectors were used for performing 2-part and 3-part WBC differentials, but were incapable of performing a 5-part differential; instead, optical detectors were required for 5-part differentials. Appx2720-2721, 85:21-87:12; Appx2723-2724, 88:19-89:25; Appx2726-2728, 91:7-93:2; Appx2782, 147:8-23; Appx2828-2829, 193:14-194:5; Appx2952-2953, 26:6-27:8. Indeed, also consistent with his patent application, Roche testified that Sysmex's (formerly known as TOA) early analyzers used electrical detector measurements for differentiating WBCs. Appx2715, 80:8-11; Appx2718-2720, 83:14-85:1.

Second, the '351 specification expressly identifies U.S. Patent No. 5,555,196 ("Asano") as an exemplary type of particle classification. Appx66, 10:29-30. Asano discloses the use of an electrical detector to count and classify monocytes and lymphocytes (i.e., mono-nucleated cells) and granulocytes (i.e., poly-nucleated cells). Appx2597, 3:4-16; Appx2597, 3:42-56; Appx2390, ¶ 120.

Third, the last paragraph of the '351 specification expressly identifies U.S. Pat. No. 5,138,181, which is Lefevre. Appx69, 16:34-38. As explained in more detail below, Lefevre discloses the use of an electrical detector alone to obtain a

differential of mono-nucleated and poly-nucleated cells (and the use of electrical resistance and optical measurements to obtain a 5-part differential).

### C. Analysis Of Body Fluids Other Than Blood

The analysis of body fluids other than blood is essential for the diagnosis of various medical conditions in adults and children such as subarachnoidal hemorrhage, meningitis, encephalitis, or a leukemic cerebrospinal fluid infiltration. Appx62, 1:27-44; Appx1900; Appx62, 1:26-44; Appx63, 3:61-4:19. In some body fluids, such as cerebrospinal fluid, the presence of only a very few blood cells can indicate a serious illness. Appx63, 4:6-15; Appx1211; Appx2348, ¶ 43. For many years, body fluid analysis was performed by a person manually counting cells in a body fluid sample on a slide under a microscope. Appx1211. This manual procedure was long-considered the gold standard, but it had several disadvantages such as low precision, high cost, delayed results, and the requirement of skilled personnel. Appx1901; Appx2353, ¶ 54.

### D. The Solution Provided by the ’351 Patent

The ’351 patent discloses the novel approach of adding to a blood analyzer, a separate mode of operation for measurement for certain types of body fluids that contain very few cells in a sample. Appx62, 1:19-35; Appx62, 2:1-18; Appx63, 3:51-4:19. The analyzer can be used for measurements of both blood samples and body fluid samples. Appx63, 3:51-58. However, as explained in more detail below,

the sequence of operations in the body fluid mode differs from the sequence of operations in the blood mode to account for the substantially lower number of blood cells present in a body fluid measurement, which requires a much greater degree of accuracy than a blood measurement. Appx66-68, 9:4-13:18.

## II. U.S. PATENT NO. 10,401,351

### A. Claim 7 of the '351 Patent

Claim 7 of the '351 patent is illustrative of the issues in the current appeal and is reproduced below, with emphases added to limitations of the claim that are discussed further below:

A sample analyzer comprising:

a plurality of detectors comprising at least one optical detector for optically sensing cells in a sample and at least one electrical detector for electrically sensing cells in the sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, *wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse*;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring cells in the body fluid sample, and wherein a respective sequence of operations for measuring cells in the blood sample and in the body fluid sample comprises (a) a sensing operation comprising operations of preparing for measurement and operating a detector to sense cells in the sample and (b) an analyzing operation comprising operations of analyzing measurements from the sensing operation and displaying analysis results, and further wherein the

plurality of detectors include one or more multi-mode detectors configured to operate in both the blood measuring mode and body fluid measuring mode,

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise concurrent display of a blood sample option and a body fluid sample option each independently selectable from the other on the input screen and (2) one or more test modes displayed separately from a selected one of the at least two sample-type options;

in response to (I) a user input, on the input screen, of selecting the blood sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting one test mode from the displayed one or more test modes, perform the sensing operation in the blood measuring mode to: prepare a blood measurement sample from the blood sample; introduce at least part of the prepared blood measurement sample into an optical detector; and *operate the optical detector to optically sense white blood cells in the introduced blood measurement sample*, and further perform the analyzing operation in the blood measuring mode to: analyze blood-sample measurements of the white blood cells sensed in the introduced blood measurement sample; *count each of five types of white blood cells based on the analyzed blood-sample measurements;* and display a count of each of the five types of white blood cells; and

in response to (I) a user input, on the input screen, of selecting the body fluid sample option from the displayed at least two test-sample options and (II) an additional user input, on the input screen, of setting said one or a different test mode from the displayed one or more test modes, perform the sensing operation in the body fluid measuring mode to: prepare a body fluid measurement sample from the body fluid sample; introduce at least part of the prepared body fluid measurement sample into an electrical detector; **operate said electrical detector to electrically sense cells in the introduced body fluid measurement sampl***e*, and further perform the analyzing operation in the body fluid measuring mode to: analyze body fluid-sample measurements of cells sensed in the introduced body fluid measurement sample; **count mono-nucleated cells and poly-nucleated cells** based on the analyzed body fluid sample measurements; and separately display in a screen a count of the mono-nucleated cells and a count of the poly-nucleated cells.

Appx64-65.

The terms in bold font above are particularly pertinent to the written description issue here. The Board summarized these limitations as "a controller programmed to analyze the cells in a body fluid measurement sample that were sensed by an electrical detector, and then count the mono-nucleated cells and poly-nucleated cells" (in other words, a 2-part differential). Appx18. The italicized terms are particularly pertinent to the obviousness issue here. The claim includes a "consisting of" limitation, which restricts the scope of the claim to seven specific types of body fluids. The claim also requires an optical detector for counting the five types of white blood cells (i.e., a 5-part differential) in the blood measuring mode.

Sysmex's arguments on the written description and obviousness issues will only address claim 7, because the remaining claims 8-15 depend on claim 7. If claim 7 has a sufficient written description, so do claims 8-15. If claim 7 is not rendered obvious, none of claims 8-15 can be rendered obvious.

### B. The '351 Specification

The '351 patent specification explains that the preferred embodiment of the invention is an analyzer that performs analytical measurements of blood samples, and analytical measurements of particular types of body fluids other than blood, such as cerebrospinal fluid. Appx63, 3:49-4:19. These types of body fluids usually

contain very few cells to detect. *Id.* The '351 patent teaches that a blood measuring mode and a body fluid measuring mode are separate measuring modes that comprise different operations. Appx66-68, 9:4-13:18.

The '351 specification describes several differences between a blood measurement mode and a body fluid measurement mode. The blood measurement mode is set as the initial operation mode of the sample analyzer. Appx66, 9:4-8. The sequence of operations in the blood measurement mode are shown on the left side of Fig. 7 and the sequence of operations for the body fluid measurement mode are shown on the right side of Fig. 7 (below). Appx51, Fig. 7; Appx65-66, 8:56-9:11; Appx66, 9:40-10:52; Appx66-68, 10:53-13:18. When switching from blood measurement mode to body fluid measurement mode, the measuring unit runs a pre sequence process (step S10) to prepare for the body fluid measurement by reducing the carryover of residual cells from the prior blood sample. Appx66-67, 10:53-12:3; Appx51, Fig. 7 (steps S9, S10); Appx63, 3:24; Appx52, Fig. 9 (flow chart showing the pre sequence steps). The pre sequence includes a "blank check operation," i.e., measurement of a blank sample that contains neither blood nor body fluid. Appx62, 2:49–55; Appx67, 11:5-10; Appx67, 11:38-12:3.

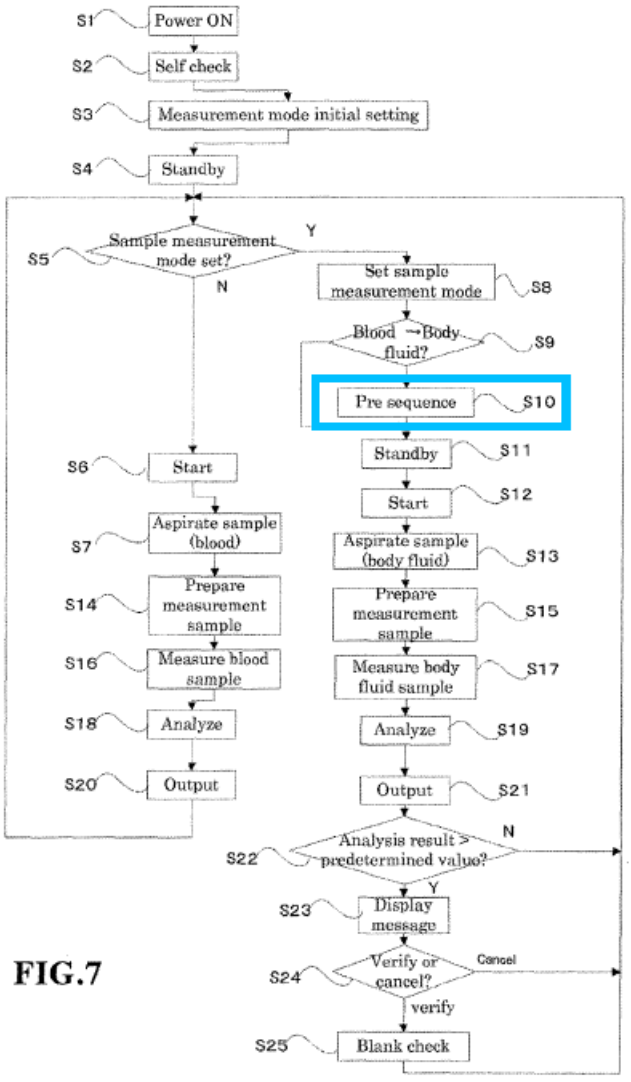


FIG.7

The ’351 specification explains that the blank check standard of the pre sequence is “more strict” than the standard of the blank check performed after “power on” and “automatic wash” in blood measurement mode. Appx67, 11:5–10. The pre sequence is not performed when switching from body fluid measurement mode to blood measurement mode, nor is it performed between samples in body fluid measurement mode because the low number of cells in a body fluid sample do

not present a carryover effect. Appx67, 11:10–17. When the blank check measurement result is not less than a predetermined tolerance value, the operator may elect to execute an automatic washing step before the blank check is repeated. Appx67, 11:17–12:3; Appx53, Fig. 9 (steps S34–S38).

In addition to the pre sequence, the ’351 specification describes other steps that are performed in the body fluid measuring mode of the preferred embodiment, such as a longer measurement time of a body fluid sample. Appx67, 12:26–40. The ’351 specification also discloses that, in blood measurement mode, white blood cells can be classified into five types (i.e., lymphocytes, monocytes, basophils, eosinophils and neutrophils), whereas in body fluid measurement mode, white blood cells are classified into two types (i.e., mono-nucleated and poly-nucleated). Appx67, 12:48–57.

With respect to the analyzer components of the preferred embodiment, the ’351 specification explains that the “sample analyzer 1 is provided with a measuring unit 2 which has the function of measuring blood and body fluid samples. . . .” Appx63, 4:20-22. Figure 2 (reproduced below) is a block diagram of the measuring unit 2. Appx63, 4:29-30; Appx2384-2385, ¶ 111.

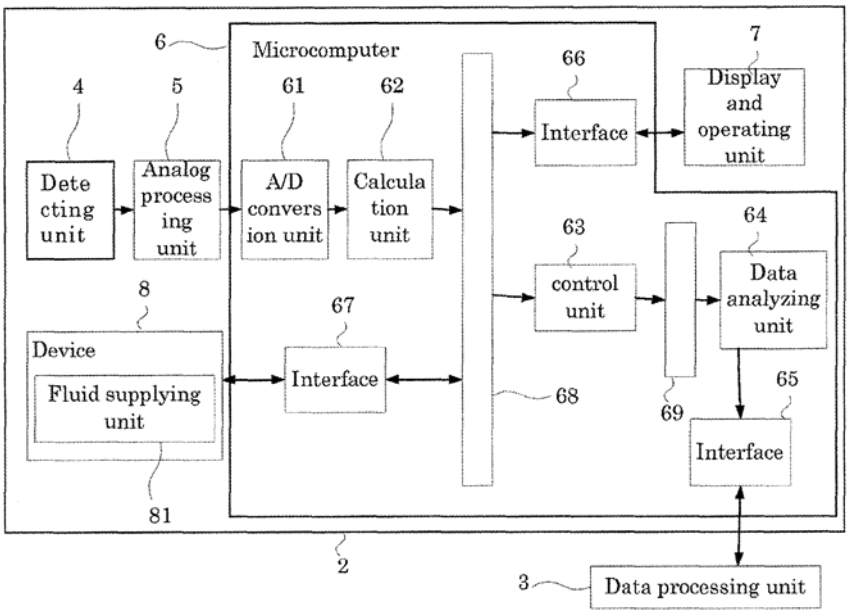


**FIG.2**

The measuring unit 2 includes a blood cell detecting unit 4. Appx63, 4:30-31. The detection device 4 is provided with a white blood cell detection unit 41 for detecting white blood cells, and with an RBC/PLT detection unit 42 for detecting red blood cells and platelets. Appx64, 5:62-6:3. A POSA reading the specification would know that the two most common types of devices for detecting red or white blood cells are electrical detectors and optical detectors, whose structure and function were well known in the art for many years. Appx2384-2385, ¶ 111.

### C. Prosecution History of the '351 Patent

It is undisputed that the '351 patent claims priority through a chain of applications dating back to 2008. The first U.S. application in the chain of priority was filed on January 31, 2008, and issued as U.S. Patent No. 8,440,140. Appx62,

1:4-14. The FWD refers to this patent as the Nagai reference. Appx8. The '351 patent is based on series of continuation applications that share the same the specification as Nagai.[2] Appx62, 1:4-14.

During prosecution of the original 2008 application, the Examiner rejected claims in the application for failing to comply with the §112, ¶ 1 written description requirement.[3] Appx2472; Appx2481. However, in the parent to the '351 application, the Examiner did not raise a written description rejection for claims that contained the limitation "electrically sense cells in the body fluid sample . . . and counting each of the mono-nucleated and poly-nucleated cells in the introduced body fluid sample". Appx2488; Appx2492; Appx2501. Nor did the examiner raise any written description objection during prosecution of claim 7 of the '351 patent. Appx701-703; Appx653-655.

[2] The '351 further claims priority back to two Japanese patent applications filed on February 1, 2007 and March 30, 2007. Appx62, 1:4-14. However, since the January 31, 2008 priority date is sufficient to negate Nagai and Jagtiani as prior art references, the Board and the parties relied on January 31, 2008 as the priority date for purposes of the IPR.

[3] Pre-AIA law should apply to whether the effective priority date is January 31, 2008.

## III. PROCEDURAL HISTORY

### A. The IPR Petition

Petitioner Beckman Coulter, Inc ("Beckman") filed a petition for *inter partes* review of claims 7-15 of the '351 patent on August 20, 2020. Appx167. The petition was based on two principal arguments. First, Beckman asserted that the challenged claims lacked sufficient written description to be entitled to a January 31, 2008 priority date. In particular, Beckman argued that the '351 specification did not have a sufficient written description for the "electrical detector" and "count mono-nucleated cells and poly-nucleated cells" limitations of claim 7. Appx15-16. Challenged claims 8-15 depend from claim 7, and Beckman did not allege that they lacked a sufficient written description for any reason independent of claim 7. Second, Beckman argued that if the claims were not entitled to the January 31, 2008 priority date, they were unpatentable under 35 U.S.C. § 103 over Nagai in view of Jagtiani. Appx8.

### B. The Board's Final Written Decision

On February 18, 2022, the Board issued its final written decision, finding claims 7-15 of the '351 patent unpatentable. Appx38.

The crux of the Board's decision is:

> More specifically, we find that the priority applications do not reasonably convey to a POSA that the inventors were in possession of a sample analyzer that ***both*** (1) uses an electrical detector to electrically

> sense cells in a body fluid measurement sample, ***and*** (2) from the analysis of the cells sensed by the electrical detector, counts the number of mono-nucleated cells and poly-nucleated cells in the body fluid measurement sample as required by claim 7.

Appx17 (emphases added).

The italicized words indicate that the Board found that there was a lack of written description for the combination of both an electrical detector to sense cells in body fluid (statement (1)) and a 2-part differential count of mono- and poly-nucleated cells (statement (2)), and not for the electrical detector to sense cells alone (statement (1)). There is no dispute that the '351 patent specification discloses an electrical detector that senses cells in a body fluid measurement. In fact, the Board expressly acknowledged that "the '351 patent specification teaches that the RBC/PLT detection unit electrically senses cells in the body fluid measurement sample (Ex. 1001, 7:7-40)." Appx20.

Thus, the written description issue boils down to whether the '351 patent specification reasonably conveys to a POSA that "the inventors were in possession of a controller programmed to analyze the cells in a body fluid measurement sample that were sensed by an electrical detector, and then to count the mono-nucleated cells and poly-nucleated cells." Appx18. The Board first considered a portion of the '351 specification's description of the preferred embodiment (Appx18-20), and concluded that the specification "does not teach that the RBC/PLT detection unit

electrically senses cells in that sample in order to count the number of mono-nucleated cells and poly-nucleated cells as required by claim 7." Appx20. Next, the Board considered the last two sentences of the '351 specification, and concluded that Lefevre does not disclose the use of an electrical detector alone to count mono-nucleated and poly-nucleated cells. Appx20-25.

After concluding that claims 7-15 were not entitled to a January 31, 2008 priority date, the Board concluded that Nagai and Jagtiani were prior art, and that "a POSA would have been motivated to combine the teachings of Nagai and Jagtiani in the manner proposed by Petitioner." Appx26-34.

## SUMMARY OF THE ARGUMENT

The Board's finding that Beckman established by a preponderance of the evidence that there was an insufficient written description for the challenged claims is not supported by substantial evidence because, as explained below, (a) the '351 specification discloses the use of an electrical detector to count the number of mono- and poly-nucleated cells, (b) the use of an electrical detector to count the number of mono- and poly-nucleated cells was well-known to a POSA at the time of the invention, and (c) the '351 specification identifies Lefevre as an alternative embodiment that includes the use of an electrical detector alone to count the number of mono- and poly-nucleated cells.

The Board's obviousness decision also should be vacated because the Board did not sufficiently explain and support its conclusions that (a) Jagtiani and Nagai disclose all of the elements recited in the challenged claims and (b) a POSA would have been motivated to combine Jagtiani and Nagai in the way of the challenged claims and reasonably expect success.

## ARGUMENT

### I. STANDARD OF REVIEW

The Court reviews the Board's decisions "to ensure that they are not 'arbitrary, capricious, an abuse of discretion, ... otherwise not in accordance with law ... [or] unsupported by substantial evidence.'" *Personal Web Tech., LLC v. Apple, Inc.,* 848 F.3d 987, 992 (Fed Cir. 2017) ((citing 5 U.S.C. § 706(2)(A)).

"Sufficiency of written description is a question of fact, reviewed for substantial evidence." *Arthrex, Inc., v. Smith & Nephew, Inc.,* 35 F.4th 1328, 1343 (Fed. Cir. 2022) (citing *Gen. Hosp. Corp. v. Sienna Biopharms., Inc.*, 888 F.3d 1368, 1371 (Fed. Cir. 2018)). "'[S]ubstantial evidence' review involves examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *In re Gartside*, 203 F.3d 1305, 1312 (Fed. Cir. 2000). Where the specification reasonably conveys to a POSA that the inventor had possession of at least one embodiment within the scope of the claims, the Board's decision of inadequate written description is unsupported by substantial evidence and should be reversed. *Tobinick v. Olmark*, 753 F.3d 1220, 1227 (Fed. Cir. 2014).

The Court reviews the Board's ultimate obviousness determination *de novo* and underlying fact-findings for substantial evidence. *Hologic, Inc. v. Smith & Nephew, Inc*., 884 F.3d 1357, 1361 (2018). "On the factual components of the inquiry, we ask whether a reasonable fact finder could have arrived at the agency's

decision, which requires examination of the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Personal Web.,* 848 F,3d at 991 (Fed Cir. 2017) (cleaned up).

## II. THE BOARD'S FINDING THAT THE '351 SPECIFICATION LACKS A SUFFICIENT WRITTEN DESCRIPTION IS NOT SUPPORTED BY SUBSTANTIAL EVIDENCE

The test for sufficiency of the written description requirement is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.,* 598 F.3d. 1336, 1351 (Fed Cir. 2010) (*en banc*). As explained below, the Board erred because a POSA would understand that the specification of the '351 conveys that the inventors had possession of the use of an electrical detector to count mono-nucleated cells and poly-nucleated cells and there is not substantial evidence to support the Board's finding to the contrary. *See Gartside*, 203 F.3d at 1312.

### A. The Board Erred By Disregarding Portions Of The '351 Specification That Reasonably Convey To A POSA The Use Of An Electrical Detector To Count Mono- And Poly-Nucleated Cells

In evaluating the written description requirement, the Board must make "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad,* 598 F.3d. at 1351. The Board's "failure to consider the totality of the record in assessing written description constitutes legal

error." *In re Tropp*, 748 Fed. Appx. 1022, 1023 (Fed. Cir. 2018) (citing *In re Alton*, 76 F.3d 1168, 1176 (Fed. Cir. 1996)). In this case, the Board erred as a matter of law because it did not consider all of the disclosures within the four corners of the ‘’351 specification, and it substituted its own perspective for that of a POSA. When all relevant information within the four corners of the ’351 patent is considered from the perspective of a POSA, there is insufficient evidence to support the Board's decision.

The Board erred by narrowly focusing on the preferred embodiment of the WBC detection unit, which is an optical detector, as the only way to classify different types of white blood cells. Appx18-19. However, as explained in more detail below, the Board overlooked that a POSA would understand from the totality of the ’351 specification that the inventors also were in possession of the well-known use of an electrical detector to count mono-and poly-nucleated cells. This error is reflected in the Board's failure to consider the totality of Fig. 2.

The specification discloses a blood cell detecting unit 4, which includes a WBC detection unit 41 for optically detecting white blood cells and an RBC/PLT detection unit 42 for electrically detecting red blood cells and platelets. Appx3-4; Appx18; Appx63, 4:30-31, Appx 64, 5:62-6:3; Appx67, 12:41-43. In the preferred embodiment, WBC detection unit 41 is an optical detector and RBC/PLT detection unit 42 is an electrical detector. Appx64, 6:4-6; Appx65, 7:7-12. The Board failed

to recognize that a POSA reading the specification understood that both types of detectors were well-known devices for detecting red or white blood cells, and that a POSA would not read the specification as limiting the detection of white blood cells to only by an optical detector. Appx2384-2385, ¶¶ 111-12.

The Board also failed to recognize that a POSA would understand that both the optical detector and the electrical detector alone do not classify specific types of cells. Appx2387-2388, ¶ 116. Instead, each detector senses each cell that passes through the detector and then creates a corresponding signal that is processed by electronic components to count and classify each sensed cell, including lymphocytes, monocytes and granulocytes. Appx2385-2390, ¶¶ 113-20; Appx66, 10:29-30; Appx2597, 3:4-17; Appx2597, 3:42-56. In fact, the Board expressly acknowledged that "the '351 patent specification teaches that the RBC/PLT detection unit electrically senses cells in the body fluid measurement sample (Ex. 1001, 7:7-40)."[4] Appx20.

However, the Board failed to consider that the signals output from the

[4] This finding is well supported in the '351 specification. Appx49 (Fig. 5); Appx65, 7:7-12, 7:25-40; Appx67, 12:41-48; Appx2385-2389, ¶¶ 113-117; Appx2799-2800, 164:23-165:3; Appx2800-2802, 165:24-167:5; Appx2815-2816, 180:8-181:7. Roche also confirmed that the electrical detector disclosed in the '351 patent will generate a signal for any particle passes through it including RBCs, WBCs and platelets. Appx2800-2801, 165:24-166:18; Appx2815, 180:8-23.

detecting unit 4, whether originating from an electrical detector or an optical detector, are input to the same analog processing unit 5, which "processes the output (analog signals) of the detecting unit 4." Appx63, 4:32-33; Appx2396, ¶ 136. As shown in Fig. 2 reproduced below, the same A/D converter 61 converts these analog signals to digital signals. Appx65, 8:20-22; Appx2396, ¶ 136. The output of the A/D converter 61 is sent to a calculation unit 62. Appx65, 8:22-26; Appx2396, ¶ 136 The calculation unit 62 prepares distribution data, in the form of scattergrams and histograms, based on the output of the detection device. Appx65, 8:26-29; Appx2396, ¶ 136.

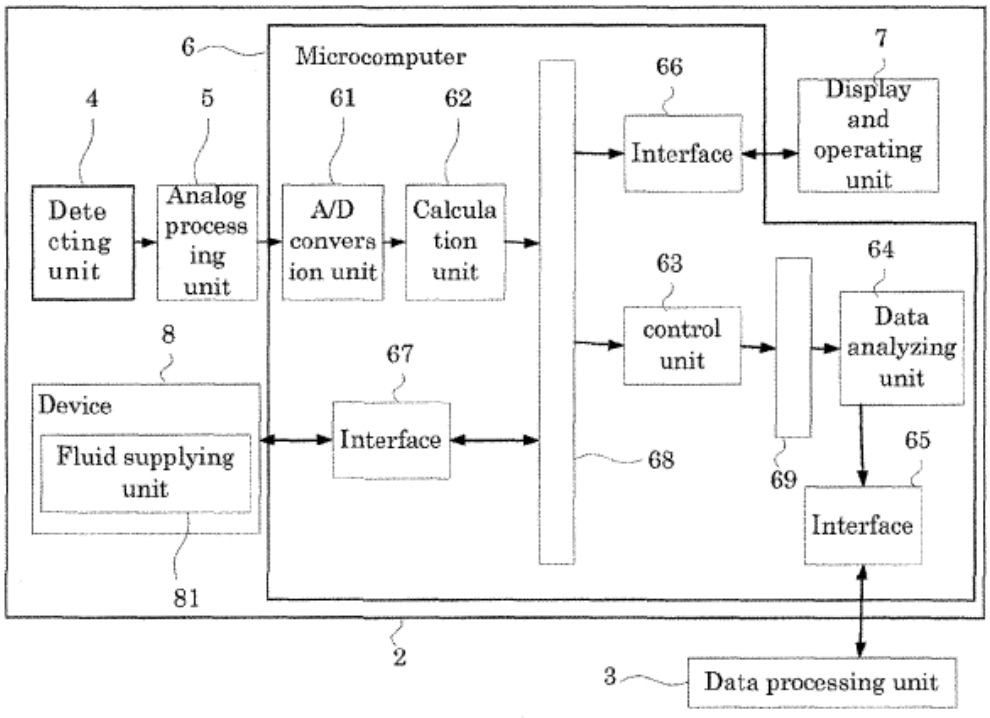


**FIG.2**

Further, Fig. 14 (below) shows the results screen for the measurement of a body fluid. Appx58; Appx68, 14:62-64. The lower-right portion depicts a histogram that shows a size distribution of RBC sensed in a body fluid sample. Appx69, 15:22-23; Appx2920, ¶ 14.

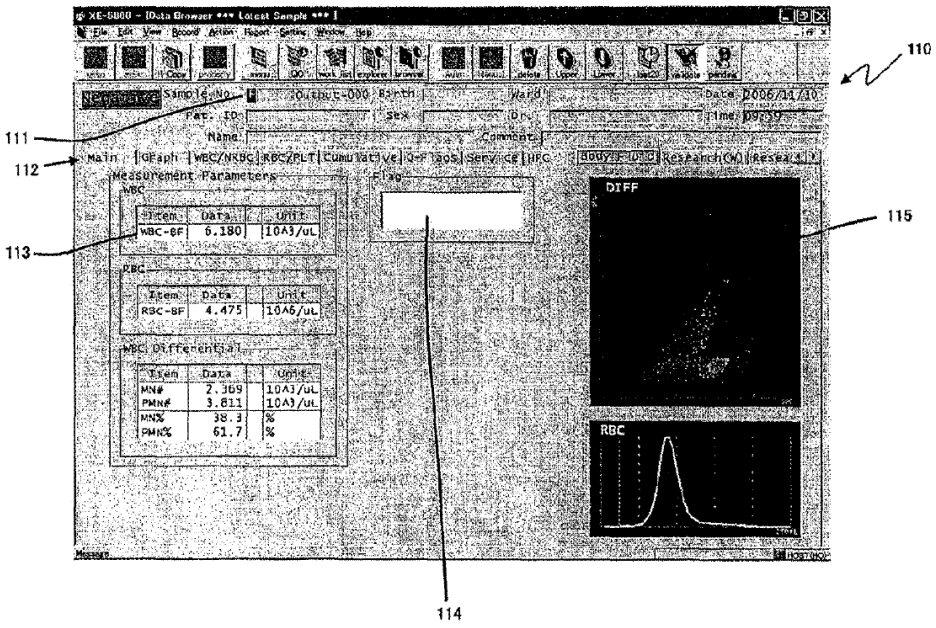


Fig.14

The Board failed to credit Dr. Robinson's unrebutted testimony that a POSA would understand, from FIGS. 2 and 14, that the signals output from electrical detector 42, whether from the detection of white blood cell or red blood cells, would be processed the same way to create the histogram such as shown in Fig. 14 that shows the size distribution of the sensed cells, which could include mono-nucleated cells and poly-nucleated cells. Appx2396-2399, ¶¶ 136-38; Appx1779, 159:13-19; Appx2920-2921, ¶¶ 14-15. The totality of the disclosures regarding Figs. 2 and 14

would convey to a POSA that the inventors were in possession of using an electrical detector to count mono-nucleated and poly-nucleated cells. *Id*.

By failing to consider the entirety of disclosures in the '351 specification from the perspective of a POSA, and Dr. Robinson's supporting testimony, the Board erred as a matter of law by its "failure to consider the totality of the record in assessing written description, *Tropp*, 748 Fed. Appx. At 1023, and by its failure to make "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art," *Ariad,* 598 F.3d. at 1351. Had the Board done so, it would have found that the '351 patent meets the written description requirement.

### B. The Board Erred By Not Accounting For Information That Was Well-known To A POSA

A patentee "can rely on information that is 'well-known in the art' to satisfy written description" unless "the four corners of the specification directly contradict information that the patentee alleges is 'well-known' to a [POSA] at the filing date." *Streck, Inc. v. Research & Diagnostic Sys*., 665 F.3d 1269, 1285 (Fed. Cir. 2012). It is well-established that a patent specification need not describe known prior art concepts. *Immunex Corp. v. Sandoz, Inc.*, 964 F.3d 1049, 1064 (Fed. Cir. 2020); *see also Zoltek Corp. v. United States*, 815 F.3d 1302, 1308 (Fed. Cir. 2016) ("The written description need not include information that is already known and available

to the experienced public."). The Court has noted that for a predictable art, a lower level of detail is required to satisfy the written description requirement. *See Hologic,* 884 F.3d at 1361.

The Board's review of the specification concluded with the following finding:

> Notably, although the '351 patent specification teaches that the RBC/PLT detection unit electrically senses cells in the body fluid measurement sample (Ex. 1001, 7:7–40), it does not teach that the RBC/PLT detection unit electrically senses cells in that sample in order to count the number of mono-nucleated cells and poly-nucleated cells as required by claim 7. Further, although the '351 patent specification teaches a WBC detection unit for sensing cells in a body fluid measurement sample in order to count the number of mono-nucleated cells and poly-nucleated cells (*id*. at 6:3–46, 12:53–60), it does not teach that the WBC detection unit is an electrical detector that electrically senses cells in that sample as required by claim 7.

Appx20. The Board erred by failing to consider the following undisputed evidence that it was well-known to a POSA to use an electrical detector to count and classify white blood cells as a 2-part differential of mono-nucleated and poly-nucleated cells.[5]

[5] The Board found that a POSA would have a high-level of education and experience in the relevant art: "Thus, we find that a POSA would have had at least a Bachelor's or Master's degree in biologic science, biomedical engineering, and/or electrical engineering or a related field and at least five years of experience in developing hardware and/or software for hematology analyzers, and would have been familiar with the design and operation of hematology analyzers available in the market. We also find that less technical education may be compensated by a higher level of experience, or vice versa." Appx11.

The Board did not account for the Roche patent application that was included in the "References Cited" section of the '351 patent. Appx41. This prior art reference explains that impedance technology (*i.e.*, an electrical detector) was able to count different types of white blood cells, but was "unable to provide a five-part differential." Appx1171, [0018]-[0019]; Appx1173, [0034] ; Appx1604, ¶ 18. Mr. Roche confirmed in his deposition that prior to 2007, a POSA knew that electrical detectors were used for performing 2-part and 3-part WBC differentials. Appx2720-2721, 85:21-87:12; Appx2722-2724, 88:19-89:25; Appx2726-27228, 91:7-93:2; Appx2782, 147:8-23; Appx2828-2829, 193:14-194:5; Appx2952-2953, 26:6-27:8.

The Board's FWD also did not mention Asano. The '351 specification expressly cites Asano, which indicates that the inventors understood its disclosures. Appx66, 29-30. The Asano reference discloses the use of an electrical detector for a 2-part differential of mono-nucleated cells (lymphocytes and monocytes) and poly-nucleated cells (a/k/a granulocytes). Appx2597, 3:4-16; Appx2597, 3:42-56; Appx2390, ¶120.

The Board addressed Lefevre, but misread that reference. As explained in detail below, Lefevre provides further evidence that the use of an electrical detector alone to count mono-nucleated and poly-nucleated cells was well-understood by a POSA prior to the 2008 filing of the U.S. application for the '351 patent. Appx1500,

1:36-40; Appx1502, 5:14-25; Appx1502, 6:36-46; Appx2392-2393, ¶128; Appx2917-2920, ¶¶ 9-13; Appx2921, ¶ 15.

Thus, the Board erred by overlooking prior art references that are cited in the '351 patent that disclose the use of an electrical detector for a 2-part differential of mono-nucleated and poly-nucleated cells was well-known to a POSA, and therefore did not need to be described in detail in the '351 specification. *Hologic*, 884 F.3d at 1363-64 (prior art references cited in the challenged patent and expert testimony evidenced the POSA's knowledge of a well-known concept); *Immunex.* 964 F.3d at 1064 (reference cited in the priority application shows a POSA would have known of the concept at the time of the invention). Indeed, nothing in the four corners of the specification contradicts the cited references and the POSA's knowledge. *Streck,* 665 F.3d at 1287 (relying on text in the specification "coupled with" what was "well-known" in the prior art to establish written description support).

### C. The Board Made Erroneous Findings Regarding Lefevre

#### 1. The Board erred by failing to understand that Lefevre discloses an alternative embodiment of using an electrical detector alone to count mono-and poly-nucleated cells

The Board erred by reading the specification's discussion of alternative embodiments and Lefevre too narrowly. "[A] specification's focus on one particular embodiment or purpose cannot limit the described invention where the specification expressly contemplates other embodiments or purposes." *ScriptPro LLC v.*

*Innovation Assocs.,* 833 F.3d 1336, 1341 (Fed. Cir. 2016); *see also Falko-Gunter Falkner v. Inglis,* 448 F.3d 1357, 1366 (Fed. Cir. 2006) ("A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before.").

The '351 specification explains that, in the preferred embodiment, scattered light and fluorescent light are used for a 5-part DIFF analysis. Appx64, 6:18-56; Appx66, 9:67-10:14; Appx67, 12:48-53. However, the last paragraph of the '351 specification explains that the inventors were in possession of alternative embodiments for their invention:

> Although white blood cells classification is performed in the body fluid measurement mode using scattered light and fluorescent light in the present embodiment, *the present invention is not limited to this configuration* inasmuch as white blood cell classification may also be performed in the body fluid measurement mode using, *for example,* scattered light and absorbed light.

Appx69, 16:17-23 (emphases added).

The last sentence of the '351 specification identifies another non-limiting example: "Furthermore, electrical resistance may be measured rather than scattered light, in which case white blood cells can be classified by the electrical resistance

and absorbed light." Appx69, 16:36-38. Thus, a POSA also would understand that "scattered light" may be replaced with electrical resistance because they represent similar parameters of a cell, and an electrical detector is used to measure electrical resistance. Appx2919-2920, ¶ 13; Appx2385-2386, ¶¶ 113-114.

Both parties' experts agreed that a POSA would have considered the last sentence of the '351 specification in the context of Lefevre. Appx1550, ¶ 85; Appx2391, ¶ 124. Lefevre explains that "[t]wo types of analysis methods are essentially known: the methods of resistivity size analysis and optical analysis methods." Appx1500, 1:19-21. Lefevre first describes the well-known use of electrical detectors to measure changes in the resistance between electrodes caused by passing white blood cells, and to generate voltage pulses that are directly proportional to the volume (i.e. size) of each cell. Appx1500, 1:22-30; Appx2391, ¶¶ 125-26; Appx2917, ¶ 9. Lefevre confirms the conventional use of electrical resistivity analysis to allow white blood cells to be differentiated according to their size into subpopulations. Appx2392-2393, ¶ 128; Appx2827-2829, 192:23-194:7 ; Appx2917, ¶ 9. Lefevre explains that this type of differentiation is "most commonly used" to approximate "three populations: the Lymphocytes, the Mononucleates and the Granulocytes." Appx1500, 1:36-40. As previously noted, a POSA would understand that granulocytes is another term for poly-nucleated cells, and that lymphocytes and monocytes are mono-nucleated cells. Appx1543-1544, ¶ 74.

Lefevre's Fig. 3 (below) is a histogram showing a distribution of white blood cells by size that were measured by the electrical detector independent of any optical measurement of the cells. Appx1502, 5:14-25; Appx1502, 6:36-46; Appx2917-2918, ¶ 10; Appx2837, 202:7-10. Lefevre describes Fig. 3 as "the presence of three distinct populations." Appx1502, 6:37-39. The far-left population is considered background noise, but the "two right-hand populations are considered as being *the whole* of the leucocytes in the sample analyzed." Appx1502, 6:44-46 (emphasis added.)

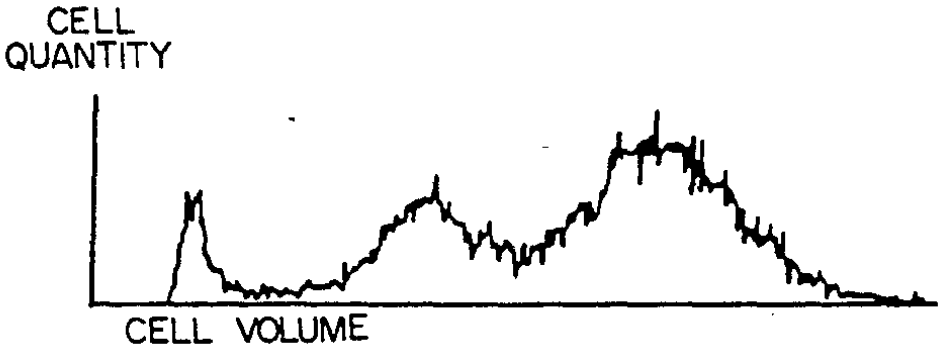


FIG.3

The explicit citation in the '351 specification to Lefevre's use of electrical resistance, which classifies "the whole of" the white blood cells into two subpopulations, conveys to a POSA that the inventors were in possession of the use of an electrical detector to count and differentiate all of the white blood cells by their size into two subpopulations as disclosed in Lefevre. Appx2917-2920, ¶¶ 9-13; Appx2392-2393, ¶ 128. Lefevre also makes clear that the white blood cell subpopulations most commonly counted by an electrical detector are mono-

nucleated cells (Lymphocytes and Mononucleates) and poly-nucleated cells (Granulocytes). Appx1500, 1:36-40. Thus, the reference in the '351 specification to the well-known teachings of Lefevre conveys to a POSA that the inventors were in possession of using an electrical detector for counting mono-nucleated and poly-nucleated cells. Appx2921, ¶ 15.

### 2. The Board made erroneous findings regarding how a POSA would understand Lefevre

The Board's decision also is not supported by substantial evidence because it relies on several erroneous findings regarding Lefevre. First, the Board states that "the '351 patent specification's reference to Lefevre is limited to what Lefevre discloses with respect to absorbed light." Appx21. The Board reads the last paragraph of the specification as narrowly limiting the alternative embodiments contemplated by the inventors to the ones expressly mentioned in the paragraph, even though the paragraph makes clear that it is describing non-limiting examples. Appx69, 16:17-37. The Board also reads Lefevre too narrowly in light of the totality of its disclosures. For example, the Board reads "white blood cells can be classified by the electrical resistance and absorbed light" as the one and only way in which they can be classified, and presumes that the inventors and a POSA are not familiar with the full teachings of Lefevre. However, Lefevre's Fig. 3 shows detection and classification of white blood cells using only electrical detection (Appx2917-2918,

¶¶ 9-10), and a POSA would understand by the explicit citation to Lefevre that the inventors also were in possession of the well-known use of an electrical detector to count mono-nucleated and poly-nucleated cells as disclosed by Lefevre.[6] Appx2918-2920, ¶¶ 12-13; Appx2921, ¶15.

The Board's statement that Lefevre teaches that "lysis of certain cell types 'frequently causes overlapping, even superimposition of the populations" is misplaced and irrelevant to the body fluid sample measurements. Appx20-22. The Board failed to recognize that Lefevre refers to lysis of blood samples, which has a high ratio of RBC to WBC, making it difficult to discriminate WBC without lysing. Appx1500, 1:30-35 ; Appx1601, ¶ 15. The Board erred by overlooking that a POSA would have understood that lysing is not required for body fluids because they contain fewer cells than blood and a lower ratio of RBC to WBC cells than blood samples. Appx62, 1:31-32; Appx63, 4:2-3; Appx1847, 227:5-16; Appx1848, 228:4-23 ; Appx1201, Table 2; Appx1201, Table 3.[7] The Board also overlooked that

[6] The Board's reliance on *Advanced Display Sys Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) is misplaced. Appx21. Sysmex never argued that Lefevre was incorporated by reference into the '351 specification. Instead, Sysmex's position is that the citation to Lefevre is evidence that the inventors had possession of technology well-known to a POSA, as this Court recognized in *Hologic* and *Immunex.*

[7] The prior art Kresie article confirms that the ratio of RBC to WBC in a body fluid sample is about 15:1. (*See* Appx1201, comparing from Table 3 the mean manual

the ’351 patent discloses that lysing is not required for the electrical detector in the preferred embodiment to separately count both RBCs and platelets, which have a higher ratio (20:1) than the (15:1) ratio of RBC to WBC in body fluids. Appx64, 5:52-57; Appx57, FIG. 13; Appx1601, ¶ 15. Finally, the Board overlooks the undisputed evidence that, even without lysing, white blood cells will generate electrical signals, which can then be processed for counting. Appx1846, 226:7-20; Appx1848, 228:4-23; Appx2800-2801, 165:24-166:14; Appx2815, 180:8-23. The Board’s failure to consider this evidence demonstrates that it erred in its reliance on Lefevre’s reference to lysing in a blood sample, because the claim limitation at issue concerns a body fluid.[8]

The Board also errs when it states: “Although Lefevre does teach using resistivity as part of its method for counting white blood cells in a blood sample, it does so *only* in conjunction with an optical method, and further criticizes using

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measured value for red blood cells in a body fluid (*i.e.*, 0.076 x $10^6$) to the Table 2 mean manual measured value for white blood cells in a body fluid (*i.e.*, 4.914 x $10^3$)

[8] The Board also misses the mark by noting that Lefevre identifies problems in classifying subpopulations of WBC using only resistivity. Appx 22. The ’351 specification notes that even when using the optical detector in the preferred embodiment, mono- and poly-nucleated cells are “classified in a partially integrated form because there are a lesser number of blood cells *and these cells are sometimes damaged.*” Appx67, 12:53-57. The ’351 patent does not require a perfect count of mono- and poly-nucleated cells.

resistivity alone to perform that function." Appx22 (Emphasis added). The first part of the Board's statement is clearly wrong because Lefevre expressly discloses counting white blood cell populations by electrical resistance alone. Appx1499, Fig. 3; Appx1500, 1:22-40; Appx1502, 5:14-25; Appx1502, 6:36-46; Appx2917-2918, ¶¶ 9-10. Indeed, Roche confirmed that Lefevre "Figure 3 shows the output just from the passing of cells through an electrical detector." Appx2837, 202:7-10. Second, the Board's characterization that Lefevre "criticizes using resistivity alone" is irrelevant because it does not negate Lefevre's disclosure of using resistivity alone to provide a two-part differentiation of white blood cells as shown in Fig. 3. Appx1502, 5:14-25; Appx1502, 6:36-46; Appx2392-2393, ¶128; Appx2917-2918, ¶ 10.

The Board overstates the significance of Lefevre's additional disclosure of optical detection. After confirming that it was well-known to use an electrical detector to count and differentiate subpopulations of mono-nucleated and poly-nucleated cells, Lefevre explains that optical methods also can be used to count a leucocyte subpopulation, but optical methods also have drawbacks. Appx1500, 1:22-40; Appx1500, 1:57-61; Appx1500, 2:23-32. Lefevre's Fig. 4 (below) shows that an optical detector alone can provide a different distribution of white blood cell populations based only on light absorption. Appx1502, 5:25-45; Appx1502, 6:46-51.

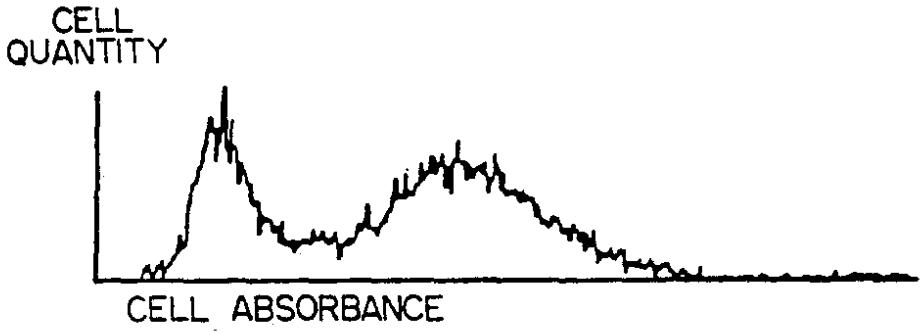



FIG.4

Lefevre's invention was to combine the results of an electrical measurement and an optical measurement of a cell to achieve the identification, counting and analysis of at least one subpopulation of WBCs and more specifically the eosinophil subpopulation. Appx1500, 2:36-41. Lefevre's Fig. 5 (below) shows that the results from the electrical detector and optical detector can be combined in a matrix format to provide the identification a specific subpopulation including the eosinophil subpopulation identified as: "PE: polynuclear eosinophils". Appx1502, 6:52-65.

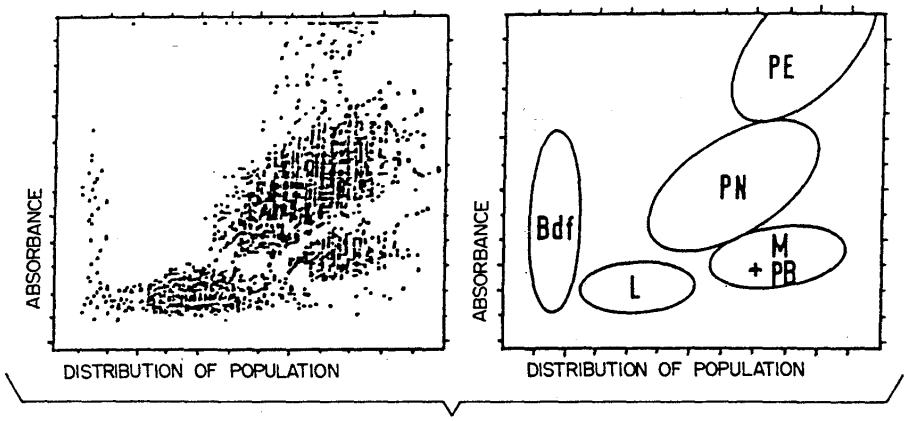



FIG.5

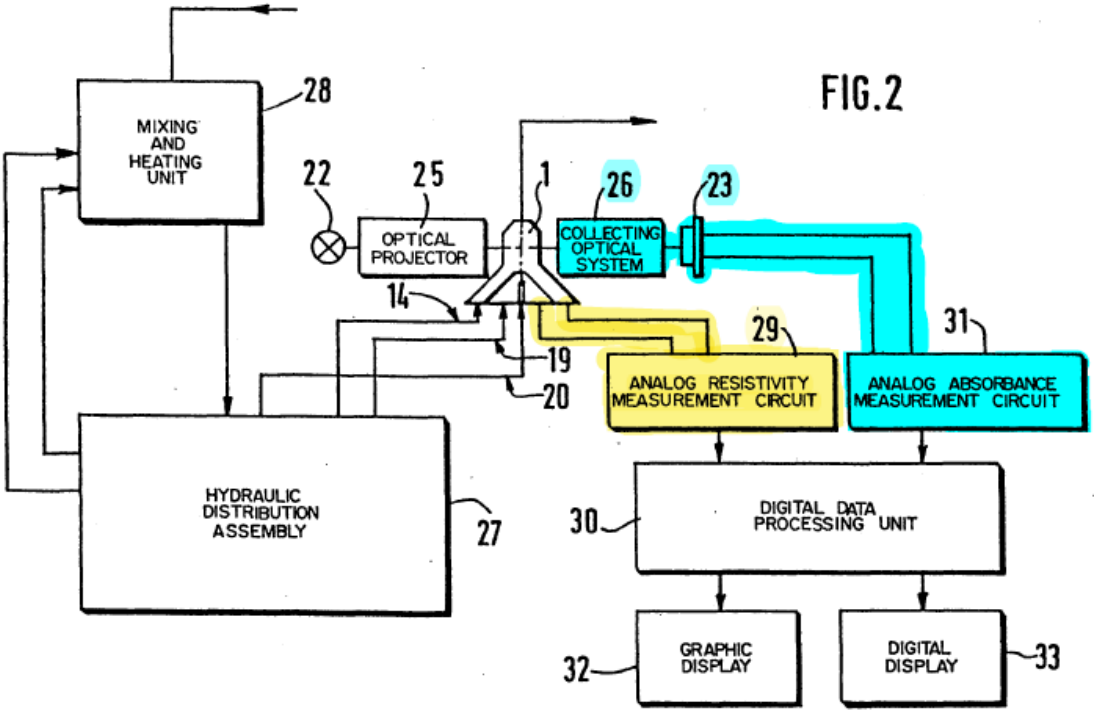
However, Lefevre's disclosures of optical measurements only in Fig. 4 and a combination of electrical and optical measurements in Fig. 5 to identify a subpopulation of eosinophils do not erase the disclosure of Fig. 3, which provides a two-part differential count of white blood cell sub-classes based only on electrical measurements. Appx1502, 5:14-25; Appx1502, 6:36-46; Appx2393, ¶ 129; Appx2837, 202:7-10; Appx2917-18, ¶ 10.[9] Moreover, a 5-part differential, like Lefevre's Fig. 5, is irrelevant because Claim 7 of the '351 patent does not require a 5-part differential for body fluid measurements; it only requires a count of mono-nucleated and poly-nucleated cells, which is a well-known 2-part differential based on electrical detector measurements that is shown in Lefevre and was well-known to a POSA. Appx71, 19:21-23; Appx2963-2964, 37:20-38:13; Appx2392-2393, ¶ 128; Appx2917-2918, ¶¶ 9-10; Appx2919-2920, ¶ 13.

Next, the Board errs in its following statement:

> Because Lefevre teaches using a detector that measures electrical *and* optical properties to analyze and classify the cells in a blood sample, it is not an "electrical detector" according to the claim construction agreed to by the parties and adopted in this case.

[9] Beckman's expert, Roche, confirms that the POSA knew that a 2-part differential of white blood cells is typically measured in impedance, but an electrical detector was unable to perform a five-part differential. Appx2720-2722, 85:21-87:12; Appx2723-2724, 88:19-89:25; Appx2726-2728, 91:7-93:2; Appx2782, 147:8-23; Appx2828-2829, 193:14-194:5; Appx1170, [0009]; Appx1171, [0019]; Appx1173, [0034] ; Appx1604, ¶18 ; Appx2952-2953, 26:6-27:8.

Appx23. The Board erred in its application of the claim construction. The Board failed to address Lefevre's Fig. 2 (below), which shows separate outputs for electrical and optical detectors. An optical detector outputs its signals to an analog absorbance measurement circuit 31. Appx1502, 6:18-22. Fig. 2 shows separate outputs from the electrical detector that are connected to a separate analog resistivity measurement circuit 29. Appx1502, 6:12-17. Lefevre also explains, with respect to its Fig. 1, that the electrodes in the orifice 12, where resistivity is measured, must be spaced apart from the optical detector light beam that generates optical pulses, so that the resistance measurements are separate from the optical measurements. Appx1502, 5:46-51; Appx1502, 5:59-61.



Placing the electrical detector and optical detector in the same housing does not mean that an electrical detector is not present in Lefevre. The governing claim construction does not require the electrical detector and optical detector to be in different housings. Indeed, the '351 patent preferred embodiment shows that optical detection unit 41 and electrical detection unit 42 are housed in the same "detection device 4." Appx64, 5:65-6:1.

Further, Lefevre fits squarely within the Board's claim constructions. The claim construction for electrical detector is a "detector that measures electrical properties, rather than optical properties." Appx13. Measuring electrical properties rather than optical properties is exactly what the electrical detector does in Lefevre:

> Counting and detection of the volume are provided by resistivity measurements. For this, a current is applied to the terminals of two electrodes situated on each side of orifice **12,** namely an anode formed by end piece **8** of the discharge duct and a cathode formed of the internal injection nozzle **16.**

Appx1502, 5:14-19. Additionally, the claim construction for optical detector is a "detector that measures optical properties, rather than electrical properties." Appx13. Measuring optical properties rather than electrical properties is exactly what the optical detector does in Lefevre:

> The optical detection, i.e. the determination of the intensity of absorption of the leucocytes, is measured by means of the light beam **24** passing through tank **5** perpendicularly to the flow to be analyzed.

Appx1502, 5:25-29.

Next, the Board errs when it states that: "Lefevre draws no further conclusions about the leucocyte population from Figure 3 and does not rely on only the information in Figure 3 to count the number of mono-nucleated cells and poly-nucleated cells in the sample." Appx23-24. However, Lefevre also discloses that it was commonly known that the subpopulations detected electrically were mono-nucleated cells and poly-nucleated cells (a/k/a granulocytes). Appx1500, 1:36-40.

Finally, the Board erroneously states that: "Taken together, the disclosures in Lefevre indicate that absorbance values from optical detection as well as volume measurements using resistivity are necessary in order to identify populations of mono-nucleated cells and poly-nucleated cells . . . . There is no indication in Lefevre that resistivity alone is sufficient to count the mono-nucleated and poly-nucleated cells in a sample." Appx24. As explained above, Fig. 5 uses a combination of electrical and optical measurements to provide a separate count of five different classifications of white blood cells; Lefevre also discloses the use of an electrical detector alone to provide a count of two different classifications of white blood cells (i.e., mono-nucleated and poly-nucleated cells). Appx1502, 6:52-65; Appx1499, Fig. 5; Appx1499, Fig 3; Appx1500, 1:22-40; Appx1502, 5:14-25, Appx1502, 6:36-46.

## III. THE BOARD ERRED AS A MATTER OF LAW WHEN IT FOUND CLAIMS 7-15 ARE OBVIOUS OVER NAGAI IN VIEW OF JAGTIANI

As explained above, the '351 specification fully satisfies the written description requirement, thereby entitling claims 7-15 of the '351 patent to the January 31, 2008 priority date. Therefore, neither Nagai nor Jagtiani are prior art to the '351 patent claims, and cannot render the claims obvious.

However, even if claims 7-15 of the '351 patent are not entitled to the January 31, 2008 priority date, the combination of Nagai and Jagtiani do not render the claims obvious for the reasons below. In addressing the obviousness issue, Sysmex will assume (without admitting) that Nagai and Jagtiani are prior art, and the priority date of the '351 patent is its March 25, 2019 filing date.

In *Personal Web*, this Court stated that under the obviousness theory presented by the petitioner there (Apple) and adopted by the Board, the Board had to make findings, supported by evidence and explanation, on two points. First, the Board had to find in the two relied upon prior art references all of the elements of the challenged patent claims, and, second, the Board also had to find that a POSA would have been motivated to combine the prior art in the way claimed by the challenged patent claims and had a reasonable expectation of success in doing so. 848 F.3d at 991. Here, the Board failed on both of these legal requirements.

### A. The Board Erred In Finding That Nagai And Jagtiani Disclosed All Elements Of Claim 7 Of The '351 Patent

The Board's obvious analysis is premised on its conclusion that Nagai does not disclose "a sample analyzer that ***both*** (1) uses an electrical detector to electrically sense cells in a body fluid measurement sample, ***and*** (2) from the analysis of the cells sensed by the electrical detector, counts the number of mono-nucleated cells and poly-nucleated cells in the body fluid measurement sample as required by claim 7. Appx17 (emphases added.) However, as explained below, Jagtiani also does not disclose using measurements from an electrical detector for counting mono-nucleated and poly-nucleated white blood cells in body fluids as required by claim 7.

Jagtiani is directed to multi-analyte detection of different enzymes or serum proteins on small volumes of blood. Appx2921, ¶ 16. Jagtiani also discloses a cartridge and system for analyzing certain types of biological samples. Appx1352-1353, [0113]. Specifically, "[e]xemplary biological samples that may be deposited into the cartridge include, but are not limited to, blood, plasma, serum, sweat, tear fluid, mucus, urine, or any other *suitable* liquid biological sample or biological sample derivative." Appx1358, [0139] (emphasis added.)

Importantly, claim 7 of the '351 patent is not drawn to any and every type of body fluid other than blood. The claim is drawn to a "body fluid, other than blood,

which is selected from a group *consisting of* cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse." Appx70, 18:20-24 (emphasis added.)

But Jagtiani does not mention a single one of the specific types of body fluids identified in claim 7. Appx1332-1469; Appx2922-2923, ¶ 18. Further, the terms "mono-nucleated cells" and "poly-nucleated cells" also are not mentioned in Jagtiani. Appx1332-1469. Thus, Jagtiani does not disclose the use of measurements from an electrical detector "to count mono-nucleated cells and poly-nucleated cells" in a "body fluid, other than blood, which is selected from a group *consisting of* cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse," as required by claim 7. Appx70, 18:20-24 (emphasis added); Appx71, 19:21-22. Jagtiani's failure to disclose the alleged missing claim elements in Nagai requires that the Board's decision on obviousness to be vacated. *Personal Web,* 848 F.3d at 993.

The Board makes several errors in attempting to fill these holes in Jagtiani. First, the Board states that "Jagtiani teaches the sensor can be configured to differentiate between and count the number of eosinophils, basophils, neutrophils, monocytes, and lymphocytes in the biological sample." Appx30. (citing paragraphs [0025] and [0121] of Jagtiani.) However, the Board relies on two paragraphs of

Jagtiani that only disclose: "*In some embodiments*, the cell count can include a white blood differential, and can include a count of basophils, a count of eosinophils, a count of lymphocytes, a count of neutrophils, and/or a count of monocytes." *Id*. (emphasis added). Neither of these paragraphs (or any other paragraph in Jagtiani) state that these types of white blood cells are counted in the particular embodiment of one of the seven specific body fluids types to which claim 7 is drawn. Notably, although Jagtiani's paragraph [0025] (Appx1339-1340) provides sixteen different examples of various things that can be done "in some embodiments," Jagtiani's 135-page disclosure does not describe or state that measurements from an electrical detector can be used to count mono-nucleated cells and poly-nucleated cells in the seven specific body fluids to which claim 7 is drawn.

Jagtiani does not disclose counting a 2-part differential of mono-nucleated cells and polynucleated cells. Significantly, when asked whether Jagtiani discloses the counting and displaying a count of mononucleated and polynucleated cells as recited in claim 7, BCI's expert, Roche, stated "**absolutely not**." Appx3064, 138:9-12. Roche's testimony establishes that there is not substantial evidence that Jagtiani discloses the missing limitation in Nagai. Nonetheless, the Board credited Roche's conclusory statement that "Jagtiani demonstrates a known technique of detecting poly-nucleated and mono-nucleated white blood cells using an electrical detector." Appx30. Roche does not identify any paragraph in Jagtiani that supports his

statement. Appx1561, ¶ 107. As explained above, Roche testified there is none. The Board's reliance on Roche's conclusory and unsupported testimony is error. *TQ Delta, LLC v. Cisco Systems, Inc*., 942 F.3d 1352, 1358-59 (Fed. Cir. 2019) ("conclusory expert testimony does not qualify as substantial evidence.")

The Board also errs to the extent it relies on Jagtiani's paragraphs [0021], [0025], [0121] and [0486] that only mention an individual count of each type of white blood cell (*i.e.*, "a count of basophils, a count of eosinophils, a count of lymphocytes, a count of neutrophils, and/or a count of monocytes") instead of a 2-part differential of mono- and poly-nucleated cells, which Roche confirmed is "absolutely not" disclosed. Appx1337, [0021]; Appx1339-1340, [0025]; Appx1354-1355, [0121]; Appx1428-1429, [0486]. The Board relied on impermissible hindsight to conclude Jagtiani discloses the counting of mono- and poly-nucleated cells in any of the seven specific body fluid types that define the scope of claim 7 of the '351 patent. *Leo Pharm. Prods. v. Rea,* 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) (reversing Board's obviousness determination because of impermissible hindsight*); cf. TQ Delta,* 942 F.3d at 1361 (cautioning against "allowing the challenger to use the challenged patent as a roadmap to reconstruct the claimed invention using disparate elements from the prior art—i.e., the impermissible ex post reasoning and hindsight bias that KSR warned against.").

Second, the Board erred by relying on the statement: "[s]uch biological samples can include, for example, blood, serum, saliva, sweat, tears, urine, or any other biological sample or derivative suspended in a fluid." Appx30 (citing ¶ 119 of Jagtiani). Here, the Board essentially concludes that Jagtiani's disclosure of the genus "any other biological sample" discloses every one of the seven specific species that define the scope of claim 7. However, Jagtiani does not explain how or why the genus "any other biological sample" or other types of biological samples disclose any one of the specific species in claim 7. *See UCB, Inc. v. Accord Healthcare, Inc.,* Nos. 16-2610, 16-2683, 16-2685, 16-2698, 16-2710, 17-1001, 890 F.3d 1313, 1325 (Fed. Cir. 2018) (prior art disclosing a genus did not render obvious a challenged claim to a species); *In re Jones*, 958 F.2d 347, 350 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract . . . the rule that . . . regardless of how broad, a disclosure of a . . . genus renders obvious any species that happens to fall within it."). Again, the Board relied on impermissible hindsight to conclude that Jagtiani's catch-all mention of "any other biological sample" discloses a count of mono-nucleated cells and poly-nucleated cells in any of the seven types of body fluids in claim 7. *Leo,* 726 F.3d at 1356-57; *cf. TQ Delta,* 942 F.3d at 1361.

Third, the Board erroneously accuses Sysmex of taking inconsistent positions. The Board overlooks significant differences between the disclosures in the '351 specification (or Nagai) and Jagtiani. As explained above, the '351 specification

expressly identifies low cell density as an attribute of the seven specific body fluid types in claim 7, and explains in detail an automated prewashing process and extended counting period to enable the accurate counting of the small number of cells in those types of body fluids. Appx63, 4:2-3; Appx66-67, 10:60-12:3; Appx67, 12:26-40; Appx2921-2922, ¶ 17. In contrast, Jagtiani makes only general, aspirational statements about "some embodiments" that are never identified; Jagtiani does not disclose why or how its electrical detector is capable of accurately detecting low cell counts in any body fluid identified in claim 7. Appx2922-2923, ¶ 18.

Finally, the Board also erred by taking inconsistent positions. It relies on Roche's unsupported statement that "Jagtiani demonstrates a known technique of detecting poly-nucleated and mono-nucleated white blood cells using an electrical detector." Appx30. As explained earlier, the use of an electrical detector to sense and classify mono-nucleated cells and poly-nucleated cells was well known prior to 2008, and a POSA would have understood that the inventors also were in possession of it. Appx2597, 3:4-16; Appx2597, 3:42-56; Appx2390, ¶120; Appx1500, 1:36-40; Appx1502, 5:14-25; Appx1502, 6:36-46; Appx2392-2393, ¶ 128; Appx2917-2920, ¶¶ 9-13; Appx2921, ¶ 15. *Streck,* 665 F.3d at 1285 (a patentee can rely on information that is 'well-known in the art' to satisfy written description.) There is no evidence that this technique only became well known after the original Nagai patent application was filed in 2008. The Board fails to explain the inconsistency of

how, on one hand, Jagtiani discloses a well-known use of an electrical detector to count and display mono-nucleated cells and poly-nucleated cells in seven specific types of body fluids, without even mentioning mono-nucleated cells, poly-nucleated cells or any of those body fluid types, but on the other hand, the '351 inventors were not in possession of that well-known technique based on the more detailed disclosures in Nagai and the knowledge of a POSA as explained above.

### B. The Board Erred In Its Analysis Of Motivation To Combine

Although the Court reviews this factual finding for substantial evidence, "[t]he factual inquiry whether to combine references must be thorough and searching, and [t]he need for specificity pervades [our] authority" on the PTAB's findings on motivation to combine." *In re Nuvasive, Inc*., 842 F.3d 1376, 1381-82 (2016) (clean). The Board's obviousness conclusion also be vacated for failure to meet this legal standard.

First, as demonstrated in the last section, the Board erroneously concluded that Jagtiani disclosed claim limitations that were allegedly not disclosed in Nagai. Even if Jagtiani were combined with Nagai, together they fail to disclose all of the limitations claim 7. Jagtiani's failure to disclose the limitations missing in Nagai provides no motivation to combine.

Second, the Board erred by "credit[ing]" Roche's testimony that a motivation to combine was found "[i]n [BCI's] DxH system, which discloses use of an electrical

detector in both a blood measuring mode and a [body][10] fluid measuring mode. Ex. 1042, ¶¶ 30, 31." Appx30-31. However, Roche testified that he never saw a DxH operate in the body fluid mode and would only be "speculating" as to how the DxH processes body fluids. Ex. 2068, 69:3-72:2. Roche's speculation is not substantial evidence.[11] *TQ Delta,* 942 F.3d at 1361-62 (conclusory and unsupported expert testimony are inadequate to support the Board's factfinding regarding motivation to combine).

Further, Roche's citation to paragraphs 30 and 31 of Sysmex's district court complaint (Appx30), which is dated September 3, 2019 (Appx1269-1270, ¶¶30-31), do not substantiate Roche's speculation. Importantly, Sysmex's allegations in a September 2019 complaint are not prior art or evidence of what was known to a POSA as of the March 2019 filing date of the '351 patent application. Appx40; *Nuvasive*, 842 F.3d at 1384 (expert's statements regarding benefits after the priority date are not evidence of a POSA's motivation to combine at the time of the invention). Moreover, paragraph 30 of the complaint simply recites a limitation

[10] The Board's quote of Roche's testimony (Ex. 1048, ¶ 107) appears to have inadvertently omitted the word the word "body" which has been reinserted above consistent with his testimony. Appx1561, ¶ 107.

[11] Further negating the Board's finding, BCI represented to the Board during oral argument that its DxH product does not use the concepts taught in the '351 patent. Appx568, 18:11-16.

from claim 1 of the '350 patent (which is not at issue in this IPR) and paragraph 31 only states: "The Accused Products include a multi-mode detector (Coulter Principle)." Appx1269-1270, ¶¶ 30-31. These paragraphs do not describe how the DxH operates and do not mention mono-nucleated cells, poly-nucleated cells or even a total number of cells as Roche's speculates. *TQ Delta,* 942 F.3d at 1361-62.

Third, the Board errs in relying on Roche's opinion that combining Nagai and Jagtiani "would simplify the number of sensors." Appx31; Appx1561, ¶ 107. Roche opines that "the proposed combination is a substitution of the electrical detector of Jagtiani for the electrical detector of Nagai." Appx1560, ¶ 105. But Jagtiani discloses several different types of electrical detectors that can be used in "some [unspecified] embodiments." *See, e.g.,* Appx1337-1338, [0021] ("In some embodiments . . . the sensor is a channel sensor . . ."; "In some embodiments, the channel sensor is a flow cytometer . . . ."; "In some embodiments, the electrical current is a multiplexed current comprising a plurality of alternating current components at different frequencies.") Jagtiani does not disclose a particular type of electrical detector to count mono-nucleated cells and poly-nucleated cells in the type of body fluids in claim 7. Roche relies on Jagtiani for a flow sensor that uses a multiplexed current with five different frequencies and real and imaginary components of impedance. Appx1556-1558, ¶ 99. This multiplexed, multi-frequency sensor is more complex than the type of electrical detector shown in Fig.

5 of the '351 specification. Appx49. Roche admits that "[t]he electrical detector disclosed in the specification of the '351 patent has only a DC component, and does not have an AC component." Appx1606, ¶ 21 Even if it were possible to replace Nagai's simple DC electrical detector with Jagtiani's complex AC electrical detector, Roche does not explain how this substitution provides any simplification, cost saving or predictable results. At a minimum, it would be necessary to add circuitry to generate alternating current, and the multiplexed, multiple frequency sensor generates much more complex results to display and interpret. [12] Appx1556-1557, ¶ 99. As in *Personal Web*, the Board's decision should be vacated because "the Board nowhere clearly explained, or cited evidence showing, *how* the combination of the two references was supposed to work." 848 F.3d at 994. The Board's obviousness decision should be vacated for failure to find that a POSA would have been motivated to combine the prior art in the way claimed by claim 7 of the '351 patent and had a reasonable expectation of success in doing so. *Id.* at 993-94.

[12] Roche also offers a proposed alternative combination of replacing Nagai's optical sensor with Jagtiani's electrical sensor, but that combination would remove the limitations in claim 7 that require an optical detector to provide a 5-part differential count of white blood cells in a blood sample. Appx70-71, 18:59-19:3. Further, Roche does not explain how replacing Nagai's optical sensor would meet the limitations of claim 7 or how it would provide simplification, cost saving or predictable results.

Fourth, the Board overlooks that despite referring to several other fluids and other unspecified "biological samples," in Jagtiani, whole blood is the only sample used for blood cell classification as shown in Figs. 22A, 22B and 22C of Jagtiani. Appx1352, [0110]-[0112]; Appx1430, [0489]; Appx2923-2924,¶ 19. Neither the Board nor Petitioner explain how or why this would motivate a POSA to combine Jagtiani with Nagai to count mono-nucleated and poly-nucleated cells in the seven types of body fluids required for claim 7. Appx2922-2923, ¶ 18.

In sum, for the foregoing reasons, Jagtiani does not disclose an electrical detector that counts mono-nucleated cells and poly-nucleated cells for any of the seven types of body fluids required by claim 7 of the '351 patent. Even if Jagtiani's flow sensor could be used for other types of body fluids, a POSA would not be motivated to combine it with Nagai for measurement of the types of body fluids required by claim 7. Appx2921-2925, ¶¶ 16-21.

## CONCLUSION

For the foregoing reasons, Sysmex respectfully requests that the Court reverse the PTAB's order that claims 7-15 of the '351 patent are unpatentable.

Respectfully submitted,

September 26, 2022

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## ADDENDUM TABLE OF CONTENTS

Trials@uspto.gov
571-272-7822

Paper 33
Entered: February 18, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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BECKMAN COULTER, INC.,
Petitioner,

v.

SYSMEX CORPORATION and SYSMEX AMERICA, INC.,
Patent Owner.

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IPR2020-01503
Patent 10,401,351 B2

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Before CHRISTOPHER L. CRUMBLEY, JO-ANNE M. KOKOSKI, and ELIZABETH M. ROESEL, *Administrative Patent Judges.*

KOKOSKI, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
*35 U.S.C. § 318(a)*

# I. INTRODUCTION

We have jurisdiction to conduct this *inter partes* review under 35 U.S.C. § 6, and issue this Final Written Decision pursuant to 35 U.S.C. § 318(a). For the reasons that follow, we determine that Beckman Coulter, Inc. ("Petitioner") has shown by a preponderance of the evidence that claims 7–15 ("the challenged claims") of U.S. Patent No. 10,401,351 B2 ("the '351 patent," Ex. 1001) are unpatentable.

## *A. Procedural Background*

Petitioner filed a Petition to institute an *inter partes* review of claims 7–15 of the '351 patent. Paper 1 ("Pet."). Sysmex Corporation and Sysmex America, Inc. (collectively, "Patent Owner") filed a Preliminary Response. Paper 6. Pursuant to 35 U.S.C. § 314(a), we instituted an *inter partes* review of claims 7–15 on the ground advanced in the Petition. Paper 10 ("Institution Decision" or "Dec."), 7, 29–30.

After institution of trial, Patent Owner filed a Patent Owner Response ("PO Resp.," Paper 15), Petitioner filed a Reply ("Pet. Reply," Paper 18), and Patent Owner filed a Sur-reply ("Sur-reply," Paper 24). We held an oral hearing on December 1, 2021, and a transcript is included in the record. Paper 32 ("Tr.").

## *B. Real Parties-in-Interest*

Petitioner identifies Beckman Coulter, Inc. as the real party-in-interest. Pet. 3. Patent Owner identifies Sysmex Corporation and Sysmex America, Inc. as the real parties-in-interest. Paper 5, 1.

## *C. Related Matters*

The parties indicate that the '351 patent is involved in the following proceeding: *Sysmex Corp. v. Beckman Coulter, Inc.*, Case No. 1:19-cv-01642-RGA-CJB (D. Del.). Pet. 3; Paper 5, 1.

*D. The '351 Patent*

The '351 patent is titled "Sample Analyzer and Computer Program Product," and relates to "a sample analyzer and a computer program product capable of measuring not only blood, but also body fluids other than blood such as cerebrospinal fluid (spinal fluid), fluid of the thoracic cavity (pleural fluid), abdominal fluid and the like." Ex. 1001, code (54), 1:19–23. The sample analyzer includes a measuring unit that measures blood and body fluids and a data processing unit that obtains analysis results by processing the output from the measuring unit. *Id.* at 4:20–24. Figure 2 of the '351 patent is reproduced below.

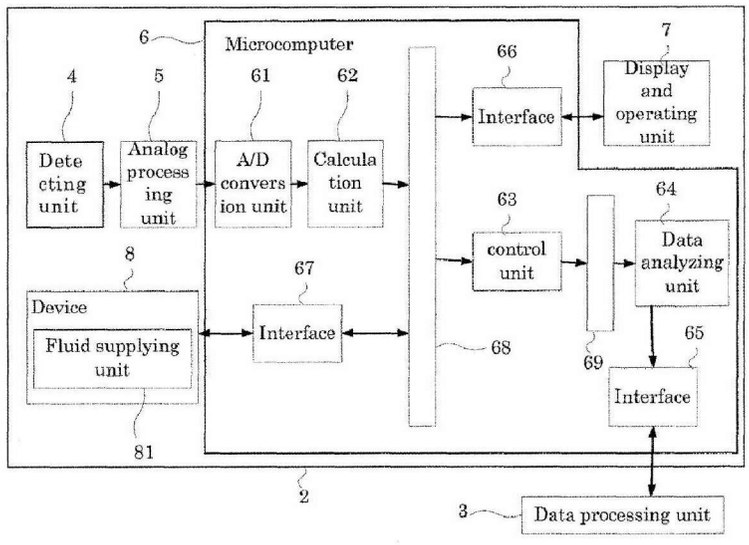


**FIG.2**

Figure 2 is a block diagram of the measuring unit of the sample analyzer described in the '351 patent. *Id.* at 3:14–15. Measuring unit 2 includes blood cell detecting unit 4, analog processing unit 5 that processes the output of detecting unit 4, microcomputer unit 6, display and operating unit 7, and device 8 for measuring blood and body fluids. *Id.* at 4:29–35. Blood cell detecting unit 4 further includes white blood cell ("WBC") detection unit 41 (not shown) for detecting white blood cells and nucleated red blood cells and

reticulocytes, and red blood cell/platelet ("RBC/PLT") detection unit 42 (not shown) for measuring the number of red blood cells and the number of platelets. *Id.* at 5:62–6:1.

The '351 patent teaches that the blood measuring mode and the body fluid measuring mode are separate measuring modes that comprise different operations. *Id.* at 9:12–39, 10:53–11:4, 11:38–13:32. "In the standby state, the operator can change the measurement mode by operating the display and operation unit." *Id.* at 9:12–14. Figure 8 of the '351 patent is reproduced below.

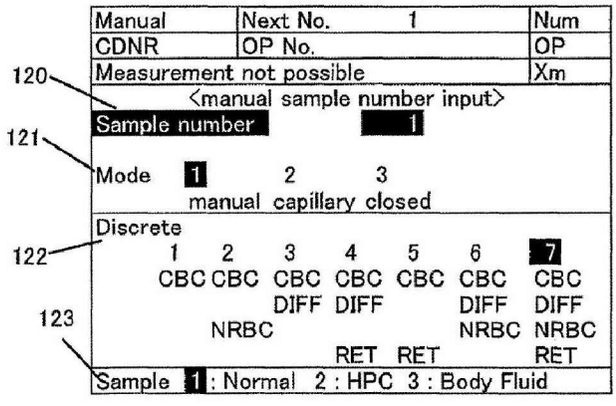


Fig.8

Figure 8 is a schematic view of the display screen for setting the measurement mode. *Id.* at 3:22–23. The screen is provided with discrete display regions including sample number 120, type of sample uptake mode 121, type of discrete test (measurement mode) 122, and type of sample 123. *Id.* at 9:15–18. Sample uptake mode 122 includes a manual mode for aspirating a sample after the sample container is manually inserted in the sample aspiration nozzle, a capillary mode for aspirating a sample via the aspiration nozzle "after the operator has previously prepared the measurement sample by mixing a sample and reagent," and a closed mode in

which the sample container is automatically transported using a conveyer device. *Id.* at 9:18–27. "The types of samples include NORMAL, which are normal blood samples; HPC, which are hematopoietic progenitor cell samples; and BODY FLUID, which are other fluids of the body." *Id.* at 9:27–30. The '351 patent explains:

> The operator can specify the sample take-up mode, measurement mode, and type of sample. When the blood measurement mode has been specified, the NORMAL sample type is specified, and an optional sample take-up mode and measurement mode are specified. When specifying the BODY FLUID measurement mode, the operator specifies MANUAL mode as the take-up mode, [CBC+DIFF], [CBC+DIFF+RET], [CBC+DIFF+NRBC], or [CBC+DIFF [+] NRBC+RET] as the DISCRETE test, and [BODY FLUID] as the type of sample.

*Id.* at 9:30–39.

When the measurement mode is switched from blood measurement to body fluid measurement mode, the measuring unit runs a pre-sequence process to prepare for the body fluid measurement that includes a blank check operation to confirm the lack of carryover effect from the blood cell components. *Id.* at 10:60–11:10. This pre-sequence is not performed when the measurement mode is switched from body fluid measurement to blood measurement because there is no carry over effect on the normal blood measurement results. *Id.* at 11:10–14.

*E. Illustrative Claim*

Petitioner challenges claims 7–15 of the '351 patent. Pet. 1, 5. Claim 7, the only independent challenged claim, is illustrative of the claimed subject matter and is reproduced below.

> 7. A sample analyzer comprising:
>
> a plurality of detectors comprising at least one optical detector for optically sensing cells in a sample and at

least one electrical detector for electrically sensing cells in the sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring cells in the body fluid sample, and wherein a respective sequence of operations for measuring cells in the blood sample and in the body fluid sample comprises (a) a sensing operation comprising operations of preparing for measurement and operating a detector to sense cells in the sample and (b) an analyzing operation comprising operations of analyzing measurements from the sensing operation and displaying analysis results, and further wherein the plurality of detectors include one or more multi-mode detectors configured to operate in both the blood measuring mode and body fluid measuring mode;

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise a concurrent display of a blood sample option and a body fluid sample option each independently selectable from the other on the input screen and (2) one or more test modes displayed separately from a selected one of the at least two sample-type options;

in response to (I) a user input, on the input screen, of selecting the blood sample option from the displayed at least two sample-type options and (II) an

additional user input, on the input screen, of setting one test mode from the displayed one or more test modes, perform the sensing operation in the blood measuring mode to: prepare a blood measurement sample from the blood sample; introduce at least part of the prepared blood measurement sample into an optical detector; and operate the optical detector to optically sense white blood cells in the introduced blood measurement sample, and further perform the analyzing operation in the blood measuring mode to: analyze blood-sample measurements of the white blood cells sensed in the introduced blood measurement sample; count each of the five types of white blood cells based on the analyzed blood-sample measurements; and display a count of each of the five types of white blood cells; and

in response to (I) a user input, on the input screen, of selecting the body fluid sample option from the displayed at least two test-sample options and (II) an additional user input, on the input screen, of setting said one or a different test mode from the displayed one or more test modes, perform the sensing operation in the body fluid measuring mode to: prepare a body fluid measurement sample from the body fluid sample; introduce at least part of the prepared body fluid measurement sample into an electrical detector; operate said electrical detector to electrically sense cells in the introduced body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze body fluid-sample measurements of the cells sensed in the introduced body fluid measurement sample; count mono-nucleated cells and poly-nucleated cells based on the analyzed body-fluid sample measurements; and separately display in a screen a count of the mono-nucleated cells and a count of the poly-nucleated cells.

Ex. 1001, 18:14–19:25.

*F. The Asserted Ground of Unpatentability*

Petitioner asserts that claims 7–15 of the '351 patent are unpatentable as having been obvious under 35 U.S.C. § 103 over the combined teachings of Nagai[1] and Jagtiani.[2] Pet. 5. Petitioner relies on the Declaration of John W. Roche (Ex. 1048) and the Supplemental Declaration of John W. Roche (Ex. 1049) to support its contentions. Patent Owner relies on the Declaration of J. Paul Robinson, Ph.D. (Ex. 2052) and the Supplemental Declaration of J. Paul Robinson, Ph.D. (Ex. 2069) to support its arguments.

## II. ANALYSIS

*A. Level of Ordinary Skill in the Art*

Factors pertinent to a determination of the level of ordinary skill in the art include "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) education level of workers active in the field." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696–697 (Fed. Cir. 1983) (citing *Orthopedic Equip. Co. v. All Orthopedic Appliances, Inc.*, 707 F.2d 1376, 1381–82 (Fed. Cir. 1983)). Not all such factors may be present in every case, and one or more of these or other factors may predominate in a particular case. *Id.* Moreover, "[t]hese factors are not exhaustive but are merely a guide to determining the level of ordinary skill in the art." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). In determining the level of ordinary skill, we may also look to the prior art, which may reflect an

[1] U.S. Patent No. 8,440,140 B2, issued May 14, 2013 (Ex. 1044).
[2] WO 2019/236682 A1, published Dec. 12, 2019 (Ex. 1045). Petitioner asserts that Jagtiani is prior art as of the Nov. 5, 2018 filing date of a provisional application to which benefit is claimed. Pet. 19.

appropriate skill level. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). Additionally, "[a] person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421.

Petitioner contends that a person having ordinary skill in the art ("POSA")

> would have possessed at least a Bachelor's or Master's degree in biologic science, biomedical engineering, and/or electrical engineering or a related field, had at least five years of experience in developing hardware and/or software for hematology analyzers, and was familiar with the design and operation of hematology analyzers available in the market, including the Sysmex XN-Series analyzers, the Beckman Coulter DxH Series analyzers and other commercially available automated hematology analyzers.

Pet. 21–22.

Patent Owner argues that a person having ordinary skill in the art "would have possessed a Bachelor's or Master's degree in biological science, biomedical and/or electrical engineering, or a related field, or would have had at least three years of experience in developing or using hardware and/or software for blood and other body fluids." PO Resp. 11 (citing Ex. 2052 ¶¶ 21–27). Dr. Robinson testifies "that someone with less technical education but more experience, or more technical education but less experience would have also met this standard." Ex. 2052 ¶ 26. Dr. Robinson further testifies that his opinions "would be the same" using Petitioner's proposed level of skill in the art. *Id.* ¶ 27.

Patent Owner argues that Petitioner's proposed skill level "could be read narrowly to only include persons with 5 or more years of industry experience developing commercial products, and to exclude others who have vast knowledge of hematology analyzers, such as academics that have

engaged in years of research, teaching and publishing in the field," and "also could exclude academics, researchers, laboratory directors and technicians who may not have personally developed a hematology analyzer, but are deeply knowledgeable about their design and operation from years of experience studying and using them." PO Resp. 12.

Petitioner replies that, because "a POSA may include persons with more technical experience in one area and less in another" and "such experience need not necessarily be limited to hematology analyzers particularly if relevant experience was obtained in other areas of medical devices," the differences between the parties' proposals regarding the level of skill of a POSA do not affect the outcome of this proceeding. Pet. Reply 3. Mr. Roche also testifies that he "considered Dr. Robinson's definition of a POSA" and "do[es] not believe that the differences between our respective positions regarding the level of skill of a POSA affect [his] opinions in this matter." Mr. Roche also agrees "that a POSA may include persons with more technical education or experience in one area and less in another, and that hardware development experience need not necessarily be limited to hematology analyzers, particularly if relevant experience was obtained in other areas of medical devices."

In the Institution Decision, we determined that Petitioner's definition was consistent with the disclosure of the '351 patent and the scope and content of the asserted prior art to the extent that Petitioner's definition requires familiarity with the design and operation of automated hematology analyzers available in the market. Dec. 8 (citing Ex. 1001, 1:45–61, 15:52–58). We also determined that Petitioner's proposal was more reasonable than Patent Owner's with respect to the duration of a POSA's practical experience, whether such practical experience is in addition to or possibly as

a substitute for an educational component, and whether a POSA's practical experience could be merely using hardware and/or software for an analyzer, as opposed to developing such hardware and/or software. *Id.* at 8–9.

Neither party contends that the differences in proposals affect the outcome of this proceeding, and we find that they do not. Nonetheless, on the full record now before us, we find that our identification of the level of ordinary skill in the art in the Institution Decision, modified to state that a higher level of experience can compensate for less technical education, is supported by the '351 patent, the prior art of record, and the opinions of Mr. Roche and Dr. Robinson (which, as discussed above, recognize that additional work experience can compensate for technical education). Thus, we find that a POSA would have had at least a Bachelor's or Master's degree in biologic science, biomedical engineering, and/or electrical engineering or a related field and at least five years of experience in developing hardware and/or software for hematology analyzers, and would have been familiar with the design and operation of hematology analyzers available in the market. We also find that less technical education may be compensated by a higher level of experience, or vice versa.

*B. Claim Construction*

We apply the claim construction standard articulated in *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005) (en banc). *See* 37 C.F.R. § 42.100(b) (2019). Under *Phillips*, the "words of a claim 'are generally given their ordinary and customary meaning,'" which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips*, 415 F.3d at 1312–13. "[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the

controversy." *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Tecs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

In the Petition, Petitioner proposes constructions for the claim terms "a controller programmed to," "optical detector," "electrical detector," and "mono-nucleated cells and poly-nucleated cells" as recited in claim 7, and "total count of nucleated cells" as recited in claims 8 and 13. Pet. 22–29. Patent Owner responds that "[t]he District Court issued an opinion regarding claim construction on April 6, 2021," and, "[f]or purposes of this proceeding, Patent Owner applies the District Court's constructions." PO Resp. 13. Patent Owner also specifically addresses the terms "controller programmed to" and "electrical detector." *Id.* at 13–14. Petitioner replies that its proposed claim constructions are consistent with the District Court's constructions. Pet. Reply 4–5. At the oral hearing, the parties confirmed that they do not dispute the District Court's claim constructions. *See* Tr. 16 (Petitioner's counsel stating that "Petitioner would request that this Board adopt these same [District Court] constructions in this IPR"), 34 (Patent Owner's counsel agreeing that "neither side has objected to the court's claim construction").

Based on the parties' apparent agreement, and considering the record before us and the Report and Recommendation from the District Court (Ex. 2065), we agree with and adopt the District Court's claim constructions. *See* 37 C.F.R. § 42.100(b) ("Any prior claim construction determination concerning the claim in a civil action . . . that is timely made of record in the *inter partes* review proceeding will be considered."). Accordingly, we construe the terms "controller programmed to," "electrical detector," and "optical detector" as set forth below.

| | |
|---|---|
| "controller programmed to" | plain and ordinary meaning |
| "electrical detector" | detector that measures electrical properties, rather than optical properties |
| "optical detector" | detector that measures optical properties, rather than electrical properties |

Ex. 2065, 13, 25–28. We determine it is not necessary to expressly construe any other claim term to resolve the parties' dispute. *Nidec Motor*, 868 F.3d at 1017.

*C. Earliest Effective Filing Date of the '351 Patent*

The '351 patent issued from U.S. Patent Application Serial No. 16/363,694 ("the '694 application"), filed on March 25, 2019 as

> a continuation of application No. 16/214,417, filed on Dec. 10, 2018, which is a continuation of application No. 15/908,339, filed on Feb. 28, 2018, now Pat. No. 10,151,746, which is a continuation of application No. 14/594,319, filed on Jan. 13, 2015, now Pat. No. 9,933,414, which is a continuation of application No, 13/891,667, filed on May 10, 2013, now Pat. No. 8,968,661, which is a continuation-in-part of application No. 12/023,830, filed Jan. 31, 2008, now Pat. No. 8,440,140.

Ex. 1001, codes (21), (22), (63). The earliest application in this chain, Application No. 12/023,830 ("the '830 application") filed on January 31, 2008, issued as Nagai. Ex. 1044, code (21); *see* Pet. 18. Petitioner contends that "[c]laims 7–15 lack adequate written description support in the applications to which the '351 patent claims priority" and "are not entitled to the benefit of the filing dates of the cited priority applications." Pet. 1.

Instead, Petitioner contends that the earliest effective filing date for the '351 patent is the March 25, 2019 filing date of the '694 application. *Id.* at 42.

"It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008); *see also Research Corps. Techs. v. Microsoft Corp.*, 627 F.3d 859, 871–72 (Fed. Cir. 2010) (holding the later-filed application, with claims that were not limited to a "blue noise mask," was not entitled to the priority filing date of the parent application, which was "limited to a blue noise mask"); *ICU Med., Inc. v. Alaris Med. Sys.*, 558 F.3d 1368, 1377–78 (Fed. Cir. 2009) (holding that "spikeless" claims "added years later during prosecution" were not supported by the specification which "describe[d] only medical valves with spikes"); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158–60 (Fed. Cir. 1998) (holding the generic shaped cup claims of the later-filed child application were not entitled to the filing date of the parent application that "disclosed only a trapezoidal cup and nothing more"). "To satisfy the written description requirement the disclosure of the prior application must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] was in possession of the invention." *PowerOasis*, 522 F.3d at 1306 (alteration in original, emphasis omitted). The sufficiency of written description support is based on "an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

Petitioner has the burden to persuade us that Nagai and Jagtiani are qualified as prior art. "In an *inter partes* review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' . . . and that burden never shifts to the patentee." *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (quoting 35 U.S.C. § 316(e)). Petitioner asserts that the combined teachings of Nagai and Jagtiani disclose each limitation of claims 7–15, and that the '351 patent is not entitled to an effective filing date before March 25, 2019. Following Petitioner's showing regarding the alleged obviousness of the subject matter of the challenged claims in view of Nagai and Jagtiani (Dec. 10–20), the burden of production shifted to Patent Owner to produce evidence and present persuasive argument based on the evidence to show that Nagai and Jagtiani are not prior art because the challenged claims are entitled to the benefit of the January 31, 2008 filing date of the '830 application. *See Dynamic Drinkware*, 800 F.3d at 1379. Petitioner has the burden of persuasion, based on all of the evidence, to prove unpatentability of the challenged claims, and this burden never shifts. *Id.*

Petitioner's contention that the challenged claims are not entitled to the January 31, 2008 filing date is based on the following limitations of claim 7:

> the controller programmed to . . . in response to . . . user input . . . introduce at least part of the prepared body fluid measurement sample into an electrical detector; operate said electrical detector to electrically sense cells in the introduced body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze body-fluid-sample measurements of cells sensed in the introduced body fluid measurement sample; count mono-nucleated cells and poly-nucleated cells based on the analyzed body-fluid-sample measurements; and separately display in a

> screen a count of the mono-nucleated cells and a count of the poly-nucleated cells.

Ex. 1001, 18:44, 19:4–25; *see generally* Pet. 32–41. Specifically, Petitioner argues that the '351 patent specification[3] "does not disclose, nor did the inventors possess, any 'electrical detector' for obtaining measurements from which the classification of white blood cells could be obtained," and does not describe "how the claimed 'controller' might classify or count mono-nucleated cells and poly-nucleated cells based on an analysis of body fluid measurements by an electrical detector." Pet. 34, 38, 40.

Patent Owner responds that the '351 patent specification provides written description support for the challenged claims, and that the claims are entitled to an effective filing date of January 31, 2008. PO Resp. 14–38. In particular, Patent Owner contends that the language of claim 7 does not limit the use of the recited electrical detector to detecting only white blood cells. PO Resp. 17–19. Patent Owner contends that the '351 patent specification "describes an embodiment of an electrical detector that electrically senses cells including red and white blood cells, in a blood sample or in a body fluid sample." *Id.* at 20 (citing Ex. 2052 ¶ 110). Patent Owner also contends that the '351 patent specification describes a detection device in the measuring unit of the analyzer that is provided with a detection unit for detecting white blood cells and a detection unit for detecting red blood cells

[3] The parties cite to the '351 patent specification to support their arguments with respect to whether the challenged claims have written description support in the priority applications. *See generally* Pet. 32–42; PO Resp. 16–38. There is no dispute that the content of the specification of Nagai (and the other applications in the '351 patent's chain of priority) and the specification of the '351 patent are the same. Pet. 18; PO Resp. 1. Therefore, we treat the parties' statements regarding a lack of disclosure in the '351 patent specification as applying equally to the priority applications.

and platelets, and that an ordinarily skilled artisan "would know that the two most common types of devices for detecting red or white blood cells are electrical detectors and optical detectors, whose structure and function were well known in the art for many years." *Id.* at 21 (citing Ex. 2052 ¶ 111).

Based on our review of the full record now before us, we determine that Petitioner has established that the priority applications do not provide adequate written description support for the challenged claims. More specifically, we find that the priority applications do not reasonably convey to a POSA that the inventors were in possession of a sample analyzer that both (1) uses an electrical detector to electrically sense cells in a body fluid measurement sample, and (2) from the analysis of the cells sensed by the electrical detector, counts the number of mono-nucleated cells and poly-nucleated cells in the body fluid measurement sample as required by claim 7.

We begin with the language of claim 7. In relevant part, claim 7 requires a controller programmed to: (1) "introduce at least part of the prepared body fluid measurement sample into an electrical detector;" (2) "operate said electrical detector to electrically sense cells in the introduced body fluid measurement sample;" (3) "perform the analyzing operation in the body fluid measuring mode to: analyze body-fluid-sample measurements of cells sensed in the introduced body fluid measurement sample;" and (4) "count mono-nucleated and poly-nucleated cells based on the analyzed body-fluid-sample measurements." Ex. 1001, 18:44, 19:13–25. In claim 7, "the introduced body fluid measurement sample" in element (2) above refers back to the part of the prepared body fluid measurement that is introduced in an electrical detector in element (1). Element (3) then requires that the analyzing operation be performed on the cells sensed by the electrical detector in the introduced body-fluid measurement sample. Accordingly, in

element (4), the mono-nucleated cells and poly-nucleated cells that are counted in the body fluid measurement sample are those that were introduced into, and sensed by, the electrical detector. Therefore, in order to prevail on its assertion that the '351 patent is not entitled to an effective filing date before March 25, 2019, Petitioner must show that the '351 patent specification, which the parties agree is the same as that in the earlier-filed priority applications, "does not convey with reasonable clarity to those skilled in the art" that the inventors were in possession of a controller programmed to analyze the cells in a body fluid measurement sample that were sensed by an electrical detector, and then to count the mono-nucleated cells and poly-nucleated cells. *See PowerOasis*, 522 F.3d at 1306.

We now turn to the '351 patent specification, which teaches that the detection device in the sample analyzer is provided with a WBC detection unit and an RBC/PLT detection unit. Ex. 1001, 5:62–6:1. The WBC detection unit is configured as an optical detection unit that uses scattered light to obtain information on the characteristics of the blood cells, such as their size and interior composition, that is then used to classify and count the cells. *Id.* at 6:18–38. The RBC/PLT detection unit is used "for measuring the number of red blood cells and the number of platelets," and is described as the "electrical resistance detection unit." *Id.* at 5:66–6:1, 12:41–44.

The '351 patent specification teaches that the WBC detection unit performs a DIFF measurement that classifies different types of white blood cells. Ex. 1001, 5:9–11 ("the sample and reagent are mixed to prepare a measurement sample for four classifications of white blood cells (DIFF)"), 9:55–57 (stating that, for blood samples, the DIFF measurement sample is measured by the WBC detection unit); 12:17–18 (same for body fluid samples). From the DIFF measurement, information is calculated for two

subclasses of white blood cells (mononuclear cells and polymorphonuclear cells) in the body fluid measurement mode, using the same classification algorithm. *Id.* at 12:48–63.

The '351 patent specification describes an example of the operation of the sample analyzer in body fluid measuring mode, wherein the body fluid sample is divided into at least a DIFF measurement sample that is measured by the WBC detection unit and an RBC/PLT measurement sample that is measured in the RBC/PLT detection unit. Ex. 1001, 12:13–25. A scattergram is obtained by measuring and analyzing the DIFF measurement sample of body fluid, and, because "fewer and damaged blood cells are contained in the body fluid, white blood cells are classified and counted as mononuclear white blood cells and polynuclear white blood cells in body fluid." *Id.* at 13:33–59. The '351 patent specification further describes displaying the results of the body fluid sample measurements in a "value display region" that

> includes the name of the measurement items for body fluid measurement rather than the measurement results for the blood measurement mode; WBC-BF (WBC count), RBC-BF (RBC count), MN# (mononuclear cell count (lymphocytes+monocytes)), PMN# (polymorphonuclear cell count (neutrophils+basophils+eosinophils), MN % (ratio of mononuclear cells among white blood cells), PMN % (ratio of polymorphonuclear cells among white blood cells), measurement values, and units are associated and displayed.

*Id.* at 15:9–18.

Accordingly, the '351 patent specification teaches that the mono-nucleated and poly-nucleated cells in the body fluid measurement sample are classified and counted based on the analysis of the DIFF measurement sample in the WBC detection unit, which the '351 patent teaches is an

optical detector. Notably, although the '351 patent specification teaches that the RBC/PLT detection unit electrically senses cells in the body fluid measurement sample (Ex. 1001, 7:7–40), it does not teach that the RBC/PLT detection unit electrically senses cells in that sample in order to count the number of mono-nucleated cells and poly-nucleated cells as required by claim 7. Further, although the '351 patent specification teaches a WBC detection unit for sensing cells in a body fluid measurement sample in order to count the number of mono-nucleated cells and poly-nucleated cells (*id.* at 6:3–46, 12:53–60), it does not teach that the WBC detection unit is an electrical detector that electrically senses cells in that sample as required by claim 7.

Patent Owner points to the last two sentences of the '351 patent specification, which cite to U.S. Patent No. 5,138,181 ("Lefevre," Ex. 1047) and state that "electrical resistance may be measured rather than scattered light, in which case white blood cells can by classified by the electrical resistance and absorbed light." PO Resp. 26 (quoting Ex. 1001, 16:35–37; citing Ex. 2052 ¶ 121). Patent Owner contends that this is "clear evidence that the inventors were in possession of the type of electrical detector disclosed in Lefevre that was used to differentiate types of white blood cells by the size of the cells," and, therefore, "the last two sentences of the '351 specification expressly discloses that the inventors were in possession of using electrical resistance to classify white blood cells." *Id.* (citing Ex. 2052 ¶ 128; Ex. 2069 ¶¶ 9–15); *see also* Sur-reply 11 (arguing that the '351 patent specification's reference "to Lefevre's use of electrical resistance to classify white blood cells shows that the inventors were in possession of this subject matter" (citing Ex. 2069 ¶¶ 9–15; Ex. 2052 ¶ 128)).

We disagree. The '351 patent specification refers to Lefevre after stating that although the described embodiment teaches that, in the body fluid measuring mode, white blood cell classification is performed using scattered light and fluorescent light, "the present invention is not limited to this configuration inasmuch as white blood cell classification may also be performed in the body fluid measurement mode using, for example, scattered light and absorbed light." Ex. 1001, 16:17–23. In particular, the '351 patent specification states that "[s]uch measurement of absorbed light is disclosed in U.S. Pat. Nos. 5,122,453 and [Lefevre]. [F]urthermore, electrical resistance may be measured rather than scattered light, in which case white blood cells can be classified by electrical resistance and absorbed light." *Id.* at 16:34–38. In this context, the '351 patent specification's reference to Lefevre is limited to what Lefevre discloses with respect to the measurement of absorbed light. *See Advanced Display Sys. Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000) (stating that, "to incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found" in the incorporated material). For this reason alone, the '351 patent's reference to Lefevre does not show that the inventors were in possession of sample analyzer that uses an electrical detector to count mono-nucleated cells and poly-nucleated cells.

Even considering Lefevre's disclosures outside of the portion identified with detailed particularity in the '315 patent specification, we are not persuaded that the reference to Lefevre demonstrates that the inventors were in possession of such a sample analyzer. Lefevre teaches that one

drawback of using resistivity to analyze and count a leucocytic[4] sub-population is "the fact that leucocytes are only differentiated by their final size," lysis of certain cell types "frequently causes overlapping, even superimposition of the populations," and that optical methods "suffer from great sensitivity of the optical alignment which means that the diffraction measurements have only relative stability." Ex. 1047, 1:49–56, 2:23–32. To avoid these problems, Lefevre teaches "an apparatus for counting and determining at least one leucocytic sub-population using at least partially an analysis and counting method by resistivity" and "at least partially an optical method" that includes measuring absorbed light. *Id.* at 2:42–54.

Although Lefevre does teach using resistivity as part of its method for counting white blood cells in a blood sample, it does so only in conjunction with an optical method, and further criticizes using resistivity alone to perform that function. Ex. 1047, 1:49–56 (stating that the main drawback of using resistivity "resides in the fact that leucocytes are only differentiated by their final size"), 2:42–54, 5:15–65 (describing the process of counting leucocytes where the solution passes through an orifice such that each cell "causes an increase of the resistivity" that creates "a voltage pulse proportional to the volume of the leucocyte," then a light beam passes perpendicularly through the flow of the solution and each cell passing through the light beam "causes a reduction of the light intensity" proportional to the intensity of its absorption, and stating that, "[t]o be taken into account, a blood cell must, previous to the optical measurement, be measured resistively by the passage through calibrated orifice 12). As set forth above, the term "electrical detector" in claim 7 means a "detector that

[4] White blood cells are also known as "leucocytes."

measures electrical properties, rather than optical properties." *See* Section II.B, *supra*. Because Lefevre teaches using a detector that measures electrical *and* optical properties to analyze and classify the cells in a blood sample, it is not an "electrical detector" according to the claim construction agreed to by the parties and adopted in this case. For these reasons, we disagree that the '351 patent specification's reference to Lefevre is "clear evidence that the inventors were in possession" of an electrical detector that senses cells in body-fluid measurement sample that are then analyzed to count the mono-nucleated cells and poly-nucleated cells as recited in claim 7.

Patent Owner also argues that "Lefevre's Fig. 3 graphically demonstrates that a POSA knew before 2008 that the type of impedance-based electrical detector disclosed in Lefevre was used to sense and classify white blood cells." Sur-reply 11. Lefevre Figure 3 is reproduced below.

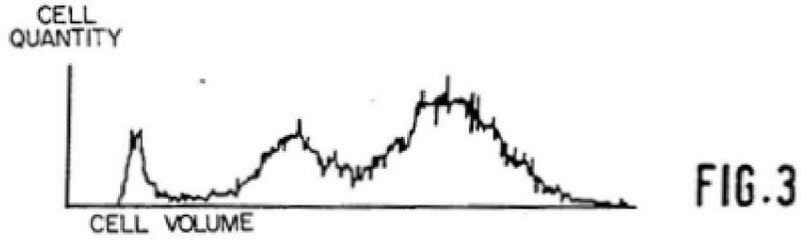


Figure 3 shows a three-peaked curve representing a size distribution of leucocytes analyzed using resistivity, with the cell quantity on the y-axis and cell volume on the x-axis. Ex. 1047, 6:36–39. Lefevre explains that Figure 3 shows three distinct populations: the most leftward portion of small sized particles considered to be background noise, and two right-hand populations "considered as being the whole of the leucocytes in the sample analyzed." *Id.* at 6:39–46. Lefevre draws no further conclusions about the leucocyte population from Figure 3 and does not rely on only the

information in Figure 3 to count the number of mono-nucleated cells and poly-nucleated cells in the sample.

Figure 5 of Lefevre is reproduced below and shows absorbance values obtained from optical detection.

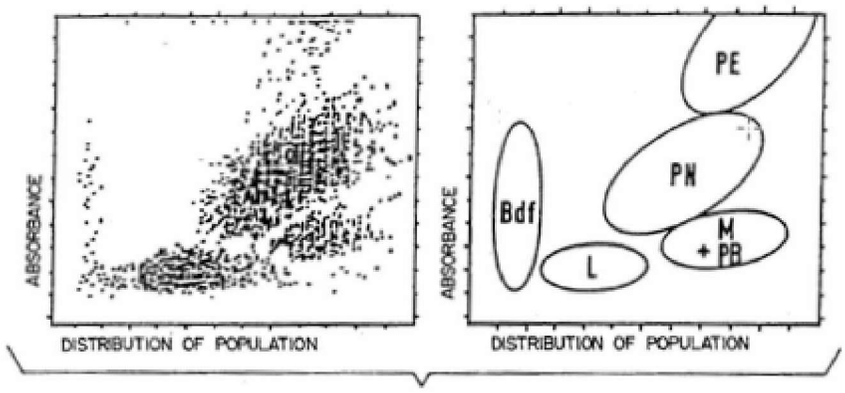


FIG. 5

Figure 5 is a matrix graphic representation showing the size distribution of the leucocyte population along the x-axis and the absorbance on the y-axis. Ex. 1047, 6:52–65. Lefevre teaches that Figure 5's representation makes it possible to identify populations of lymphocytes (L), monocytes (M), polynuclear basophils (PB), polynuclear neutrophils (PN), and polynuclear eosinophils (PE), as well as the background noise (Bdf). *Id.* at 6:55–65. Taken together, the disclosures in Lefevre indicate that absorbance values from optical detection as well as volume measurements using resistivity are necessary in order to identify populations of mono-nucleated cells and poly-nucleated cells. *Id.* at 1:49–56 (discussing drawbacks of resistivity method), 2:42–54 (cells are counted using both a resistivity method and an optical method). There is no indication in Lefevre that resistivity alone is sufficient to count the mono-nucleated and poly-nucleated cells in a sample. Accordingly, consideration of Lefevre's disclosures as a whole reinforces our finding that the '351 patent specification's reference to Lefevre does not

show that the inventors were in possession of sample analyzer that uses an electrical detector to count mono-nucleated cells and poly-nucleated cells.

Patent Owner also argues that a POSA would have understood that the '351 patent specification's description of an electrical detector that senses blood cells in a body fluid sample, and its description of analyzing and interpreting the measurement of cells sensed by an electrical detector, demonstrates that the inventors were in possession of a controller programmed to analyze cells sensed in a body fluid measurement sample by an electrical detector and to count the mono-nucleated and poly-nucleated cells therein. PO Resp. 19–20 (citing Ex. 2052 ¶¶ 107–109). Similarly, Dr. Robinson testifies that "a POSA would have been well aware that electrical detectors were capable to measure sub-classes [of] white blood cells in a measurement sample." Ex. 2052 ¶ 112 (citing Ex. 1001, 16:16–37). Dr. Robinson cites to the '351 patent specification's reference to Lefevre, which, as discussed above, does not teach an electrical detector for counting the mono-nucleated and poly-nucleated cells in a sample. Moreover, Patent Owner appears to be arguing that a person of ordinary skill in the art would have found it obvious to use an electrical detector to sense cells in a body fluid sample, and then analyze the sensed cells and count the mono-nucleated cells and poly-nucleated cells. Although the written description requirement does not require "that the specification recite the claimed invention *in haec verba*, a description that merely renders the invention obvious does not satisfy that requirement." *Ariad Pharms., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010) (citing *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571–1572 (Fed. Cir. 1997); *see also LizardTech, Inc. v. Earth Resource Mapping, Inc.*, 424 F.3d 1336, 1346 (Fed. Cir. 2005) ("[A] patentee cannot always satisfy the requirements of

section 112, in supporting expansive claim language, merely by clearly describing one embodiment of the thing claimed. . . . the description of one method . . . does not entitle the inventor . . . to claim any and all means for achieving that objective.").

For the foregoing reasons, we determine that Petitioner shows, by a preponderance of the evidence, that independent claim 7, and claims 8–15 that directly or indirectly depend therefrom, lack written description support in the '351 patent specification and its priority applications. Specifically, we find that the priority applications do not contain adequate written description for a controller programmed to analyze the cells in a body fluid measurement sample that were sensed by an electrical detector, and to count the mono-nucleated cells and poly-nucleated cells. Accordingly, we determine that Petitioner establishes, by a preponderance of the evidence, that the challenged claims of the '351 patent are not entitled to the benefit of the January 31, 2008 filing date of the '830 application, and the earliest effective filing date of the challenged claims is the March 25, 2019 filing date of the '694 application.

*D. Obviousness over Nagai and Jagtiani*

Petitioner contends that the subject matter of claims 7–15 of the '351 patent would have been obvious under 35 U.S.C. § 103[5] over the combined teachings of Nagai and Jagtiani. Pet. 42–64. Petitioner argues that Nagai is prior art under 35 U.S.C. § 102(a)(1) because it "issued on May 14, 2013, more than one year prior to March 25, 2019, which is the earliest effective

[5] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284–88, amended as 35 U.S.C. §§ 102 and 103. Because the effective filing date of the challenged claims of the '351 patent is after March 16, 2013, the post-AIA versions of 35 U.S.C. §§ 102 and 103 apply.

filing date of the '351 patent." *Id.* at 18. Similarly, Petitioner argues that Jagtiani is prior art because it "is fully supported by" a series of provisional applications and "is considered to have been effectively filed under 35 U.S.C. § 102(d)(2) as of no later than" the November 5, 2018 filing date of the last such provisional application. *Id.* at 19. As set forth above, we determine that Petitioner establishes by a preponderance of the evidence that the effective filing date of the '351 patent is not earlier than March 25, 2019. Accordingly, on the present record, we determine that Nagai is prior art under 35 U.S.C. § 102(a)(1) because it issued more than one year before the effective filing date of the '351 patent. Patent Owner does not dispute that Jagtiani is prior art to the '351 patent if the challenged claims are not entitled to a January 31, 2008 priority date. *See* PO Resp. 38.

There is no dispute that the content of Nagai and the content of the '351 patent specification is the same. Pet. 18; PO Resp. 1. Jagtiani is directed to cartridges and devices for analyzing a biological sample (such as blood, serum, sweat, tears, mucus, urine, or any other biological sample or derivative suspended in a fluid), including by "transporting the biological sample through a sensor comprising a channel or pore; applying an electrical current or voltage to the channel or pore; and determining a cell count or detecting the analyte based on the detected impedance." Ex. 1045, code (57), ¶ 113. Jagtiani teaches that different types of cartridges can be configured to perform different assays of the biological sample, such as a complete blood count ("CBC") assay that "can distinguish and count different blood cell types, such as red blood cells, platelets, and white blood cells (including eosinophils, basophils, neutrophils, monocytes, and lymphocytes)." *Id.* ¶ 113. Jagtiani also teaches that "the same controlling device can engage with the different cartridges, allowing for a single

versatile device that can be used to perform a plurality of assays by interfacing with a selected cartridge." *Id.*

*1. Motivation to Combine Nagai and Jagtiani*

In order to demonstrate obviousness, a petitioner must demonstrate that a skilled artisan would have had a reason to combine the teachings of the prior art in the manner claimed in the patent and would have had a reasonable expectation of success in doing so. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Petitioner cannot satisfy its burden of proving obviousness by employing "mere conclusory statements," but "must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016).

Petitioner contends that a POSA would have been motivated to replace Nagai's electrical detector (which measures only the number of red blood cells in determining a CBC measurement) with Jagtiani's electrical detector (which senses and analyzes cells of body fluids in order to count white blood cells) in order to "to perform both measurements of red blood cells, and of mono-nucleated cells and poly-nucleated white blood cells in body fluid measurement samples." Pet. 43–44, 54–55 (citing Ex. 1045 ¶¶ 21, 25, 119, 486; Ex. 1048 ¶¶ 102–104). Petitioner contends that modifying Nagai in this manner would yield the predictable result of using an electrical detector, instead of an optical detector, to detect mono-nucleated and poly-nucleated white blood cells in body fluid samples. *Id.* at 43–44 (citing Ex. 1048 ¶ 104). Petitioner also contends that a POSA "would have made the combination as proposed to simplify the number of sensors to be used to measure body fluid." *Id.* at 45 (citing Ex. 1048 ¶ 108).

Petitioner further contends that a POSA would have had a reasonable expectation of success in modifying Nagai as proposed. Pet. 45. Petitioner contends that, because the modification is "little more than a substitution of the electrical sensor disclosed by Nagai (or optical sensor used in the body fluid measurement mode) for the electrical sensor disclosed by Jagtiani," it "would have been well within the skill of a POSA." *Id.* at 45–46 (citing Ex. 1048 ¶ 109).

Patent Owner argues that a POSA "would not be motivated to combine Jagtiani with Nagai for the measurement of the body fluid types identified in claims 7–15 of the '351 patent." PO Resp. 43 (citing Ex. 2069 ¶ 20). In particular, Patent Owner argues that "none of the types of body fluids identified in claims 7–15 are mentioned in Jagtiani," and "Jagtiani fails to disclose how his cartridge could provide an accurate measurement of the low number of blood cells that may be present in the types of body fluid identified in claims 7–15." *Id.* at 40 (citing Ex. 2069 ¶ 18).

Based on our review of the record, we determine that Petitioner has established that a POSA would have had reason to combine the teachings of Nagai and Jagtiani to achieve the claimed subject matter. Nagai describes an electrical detector (RBC/PLT detection unit 42) that "is capable of measuring the number of red blood cells and platelets by a sheath flow-DC detection method." Ex. 1044, 6:58–63, Fig. 5. Nagai also describes WBC detection unit 41 that produces a DIFF scattergram that, in the body fluid measuring mode, is analyzed in order to classify the white blood cells into two subclasses, namely, mono-nucleated cells and poly-nucleated cells. *Id.* at 5:56–58, 12:27–36. Nagai teaches that WBC detection unit 41 is "configured as an optical detection unit" that performs white blood cell classification in the body fluid measurement mode using a combination of

scattered light and fluorescent light, scattered light and absorbed light, or electrical resistance and absorbed light. *Id.* at 5:56–58, 15:52–16:6.

Jagtiani teaches a channel sensor that can detect impedance to differentiate between different types of cells in a biological sample, including differentiating between red blood cells, white blood cells, and platelets. Ex. 1045 ¶¶ 21, 25; *see also id.* ¶ 187 ("The channel sensor is based on impedance sensing using the Coulter principle."). Jagtiani teaches the sensor can be configured to differentiate between and count the number of eosinophils, basophils, neutrophils, monocytes, and lymphocytes in the biological sample. *Id.* ¶ 25; *see also id.* ¶ 121 ("In some embodiments, the cell count can include a white blood differential, and can include a count of basophils, a count of eosinophils, a count of lymphocytes, a count of neutrophils, and/or a count of monocytes."). Jagtiani further teaches that "[s]uch biological samples can include, for example, blood, serum, saliva, sweat, tears, urine, or any other biological sample or derivative suspended in a fluid." *Id.* ¶ 119.

In light of these teachings in Nagai and Jagtiani, we credit Mr. Roche's testimony that

> Jagtiani demonstrates a known technique of detecting poly-nucleated and mono-nucleated white blood cells using an electrical detector. A POSA at the time of the invention would have been led to modify Nagai with the teaching of Jagtiani in the manner claimed to allow the body fluid measurement of Nagai to differentiate poly-nucleated and mono-nucleated blood cells (instead of measuring red blood cells alone). Such a motivation is found, for example, in Petitioner's DxH system, which discloses use of an electrical detector in both a blood measuring mode and a fluid measuring mode. Ex. 1042 ¶¶ 30, 31. In the DxH system, use of an electrical detector in both the blood measuring mode and body fluid measuring mode allows identification of total number of cells in measured body fluid.

> Thus, one having ordinary skill in the art would have made the combination as proposed to simplify the number of sensors to be used to measure body fluid.

Ex. 1048 ¶ 107. That Nagai teaches using electrical detection to analyze red blood cells and platelets, and also teaches that a combination of resistivity (electrical detection) and absorbed light (optical detection) can be used to detect and analyze white blood cells, and Jagtiani teaches using electrical detection alone to detect and analyze white blood cells, supports Mr. Roche's testimony that the proposed modification of Nagai would simplify the number of sensors used to measure a body fluid sample by eliminating the need for an optical detector. *See* Ex. 1044, 5:56–58, 6:57–62, 15:52–16:6; Ex. 1045 ¶¶ 21, 25, 119, 187; *see also Perfect Web Techs., Inc. v. Info USA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009) (A reason to combine or modify the prior art may be found explicitly or implicitly in market forces, design incentives, the "interrelated teachings of multiple patents," "any need or problem known in the field of endeavor at the time of the invention and addressed by the patent," and "the background knowledge, creativity, and common sense of the person of ordinary skill in the art." (quoting *KSR*, 550 U.S. at 418–421)).

We determine that Petitioner's showing outweighs Patent Owner's arguments and evidence. Patent Owner argues that "Jagtiani does not disclose an electrical detector that is suitable for use with the types of body fluids identified in claims 7–15 of the '351 patent." PO Resp. 43. In that regard, Patent Owner argues that Jagtiani does not identify any of the body fluids listed in the challenged claims. *Id.* at 40. Patent Owner's argument, however, overlooks Jagtiani's teaching that, in addition to the exemplary

biological fluids listed, "any other biological sample or derivative suspended in a fluid" can be analyzed by the described sensors. Ex. 1045 ¶ 119. Patent Owner does not contend that the body fluids identified in claims 7–15 are not "biological sample[s] or derivative[s] suspended in a fluid." *See* Ex. 1050, 179:13–181:20 (Dr. Robinson testifying that the term "biological fluids" as used in Jagtiani would include the body fluids identified in the challenged claims).

Patent Owner also argues that "Jagtiani was not designed to have the type of accuracy required for the body fluids listed in claims 7–15." PO Resp. 40. In particular, Patent Owner argues that Jagtiani "fails to disclose" how its detectors "could provide an accurate measurement of the low number of blood cells that may be present in the types of body fluids identified in claims 7–15." *Id.* However, like the body fluids identified in the challenged claims, some of the specific biological samples enumerated in Jagtiani also contain a low number of blood cells. Ex. 1049 ¶ 37; Ex. 1050, 183:16–187:4. Moreover, Jagtiani teaches that "[t]he channel sensor is based on impedance sensing using the Coulter principle." Ex. 1045 ¶ 187. Patent Owner's argument that Jagtiani's electrical detector is unsuitable for detecting blood cells in biological samples with a low count of blood cells is inconsistent with its assertion that a "POSA would have readily understood" that Nagai's electrical detection unit 42 "was an example of the well-known Coulter principle type of electrical detector for measuring various types of cells, including white blood cells," and that Nagai "is explicitly directed to providing an accurate count of blood cells in the types of fluids with very few cells." PO Resp. 22, 41 (citing Ex. 2052 ¶ 113; Ex. 2069 ¶ 18). In view of this inconsistency, we give little credence to Patent Owner's argument that Jagtiani's electrical detector, which

operates on the same principle as the electrical detector in the '351 patent, was not designed to have the accuracy required for the types of body fluids recited in the challenged claims.

We also do not agree with Patent Owner that "Jagtiani teaches away from using an electrical detector for measuring white blood cells in the types of body fluids identified in Claims 7–15." Sur-reply 22 (citing Ex. 2069 ¶¶ 16–21). "Under a proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosure are unlikely to produce the objective of the [patented] invention." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citing *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Patent Owner does not direct us to any statements in Jagtiani that criticize or discredit the use of an electrical detector to measure white blood cells in body fluids with low white blood cell counts, nor anything that would discourage the use of an electrical detector to count white blood cells in the types of body fluids identified in the challenged claims. On the contrary, Jagtiani does not limit the types of biological samples that can be used with its analyzer, stating that they "can include, for example, blood, serum, saliva, sweat, tears, mucus, urine, or any other biological sample or derivative suspended in a fluid." Ex. 1045 ¶ 119. Furthermore, the evidence shows that, like the body fluids recited in the challenged claims, some of the biological samples that Jagtiani specifically names also have a low blood cell count. Ex. 1049 ¶ 37; Ex. 1050, 183:16–187:4. Jagtiani also explicitly states that "the cell count can include a white blood differential, and can include a count of basophils, a count of eosinophils, a count of lymphocytes, a count of neutrophils, and/or a count of monocytes," with no qualification as to the types of biological samples that can be analyzed in this manner. Ex. 1045 ¶ 121.

We have considered Patent Owner's argument and Dr. Robinson's testimony that a POSA would have understood that it would take Jagtiani at least 90 minutes "to complete the analysis of the types of body fluids identified in claims 7–15," and that "[t]his amount of time is not suitable for these types of body fluids when results are needed rapidly while patients are in surgery or undergoing other invasive medical procedures." PO Resp. 42–43; Ex. 2069 ¶ 20. Neither Patent Owner nor Dr. Robinson direct us to any statements in Nagai that the results from the body fluid sample analysis "are needed rapidly" such that a POSA would be discouraged from looking at a reference such as Jagtiani to improve Nagai's sample analyzer. In addition, Dr. Robinson's 90 minute estimation is based on his analysis of one of Jagtiani's examples that was directed to detecting cells in a whole blood sample. *Id.* ¶ 19; Ex. 1045 ¶¶ 489–490. Dr. Robinson, however, could not confirm that the flow cytometer detector in this example was an electrical detector, and testified that it "uses both electrical and optical detectors." Ex. 1050, 210:2–212:11. Dr. Robinson also testified that "there is no information" in the figures he relied on to support his 90 minute estimation "as to exactly how they made those measurements." *Id.* at 213:23–214:7. Furthermore, even if rapid results are sometimes required, there is no evidence that is always the case. Consequently, we give little weight to Dr. Robinson's testimony in this regard.

For these reasons, after considering Petitioner's and Patent Owner's positions as well as the supporting evidence, we determine that Petitioner has established that a POSA would have had sufficient reason to combine the teachings of Nagai and Jagtiani in the manner proposed by Petitioner.

*2. Claims 7–15*

Petitioner contends that Nagai teaches or suggests all of the elements of independent claim 7, except for the use of an electrical detector to electrically sense cells in the body fluid measurement sample, and the analysis of those sensed cells to count the number of mono-nucleated cells and poly-nucleated cells in that body fluid measurement sample. Pet. 46–54, 57–58. Petitioner contends that "Jagtiani discloses the use of an electrical detector to sense and analyze cells of body fluids" and "to count white blood cells in a body fluid sample." *Id.* at 54–55 (citing Ex. 1045 ¶¶ 21, 25, 119, 486). Petitioner contends that "[a] POSA would have understood that Nagai's electrical detector measures only the number of red blood cells in determining a CBC measurement," and would have replaced Nagai's electrical detector with Jagtiani's electrical detector "to perform measurements of red blood cells, and of mono-nucleated cells and poly-nucleated white blood cells in body fluid measurement samples." *Id.* at 43 (citing Ex. 1048 ¶¶ 102–104). Petitioner provides a claim chart identifying where each element of claim 7, and claims 8–15 that depend therefrom, can be found in Nagai and Jagtiani. *Id.* at 46–64.

Other than the arguments with respect to the suitability of Jagtiani's electrical detector for use with the body fluids identified in claim 7 addressed above, Patent Owner does not otherwise dispute Petitioner's evidence that the combined teachings of Nagai and Jagtiani disclose the limitations of claims 7–15. PO Resp. 38–43; Sur-reply 19–22.

Having reviewed Petitioner's assertions regarding claims 7–15, as well as the supporting evidence, we determine on this record that Petitioner has established by a preponderance of the evidence that the combined

teachings of Nagai and Jagtiani account of all the limitations recited in claims 7–15. Pet. 46–64; Ex. 1045 ¶¶ 116–137.

*3. Mr. Roche's Testimony*

Patent Owner argues that "[t]he weight given to Petitioner's expert should be deeply discounted" because Mr. Roche "was shielded during his deposition" by "Petitioner's excessive, improper objections." PO Resp. 44–46 (citing *Ericsson Inc. v. Intellectual Ventures LLC*, IPR2014-01149, Paper 68 at 8–10 (PTAB Dec. 9, 2015)). In particular, Patent Owner argues that Petitioner's counsel repeatedly objected "to questions as 'outside the scope of the declaration,' when clearly they were not." *Id.* at 44. Petitioner responds that "Patent Owner's own expert repeatedly refused to answer questions within the scope of his report" and "the questions put to Petitioner's expert were frequently beyond the scope of the witness's declaration." Reply 8 n.2.

On this record, we decline to generally discount the weight given to Mr. Roche's testimony based on Petitioner's counsel's objections during Mr. Roche's deposition. As an initial matter, Patent Owner does not contend, nor do we find, any instances where Mr. Roche was instructed by Petitioner's counsel to not answer Patent Owner's questions based on the objections. Additionally, our Consolidated Trial Practice Guide advises that, at any time during the testimony, a party may move to terminate or limit the testimony on the ground that it is being conducted in bad faith, and the testimony may be "suspended for the time necessary to obtain a ruling from the Board." PTAB Consolidated Trial Practice Guide, App. D at 130 (Nov. 2019), https://go.usa.gov/xpvPF. Despite Patent Owner's concerns regarding the propriety of Petitioner's counsel's objections, Patent Owner did not avail itself of this option during Mr. Roche's deposition.

Additionally, this case is distinguishable from *Ericsson*, where the Board discounted a declarant's testimony because the proponent of the testimony shielded the declarant from information "so that he did not address it in his declaration and was unprepared to testify about it at [his] deposition." *Ericsson*, Paper 68 at 9–10. Here, Patent Owner does not allege that Mr. Roche was shielded from any particular information, or that Mr. Roche was unprepared to testify as a result.

It is within our discretion to assign the appropriate weight to Mr. Roche's testimony. *See, e.g.*, *Yorkey v. Diab*, 601 F.3d 1279, 1284 (Fed. Cir. 2010) (holding that the Board has discretion to give more weight to one item of evidence over another "unless no reasonable trier of fact could have done so"); *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) ("[T]he Board is entitled to weigh the declaration and conclude that the lack of factual corroboration warrants discounting the opinions expressed in the declarations."). Patent Owner's contentions do not persuade us that we should generally discount Mr. Roche's testimony as requested.

## III. CONCLUSION[6]

After reviewing the record and weighing the evidence offered by both parties,[7] we determine that Petitioner has shown, by a preponderance of the evidence, that claims 7–15 of the '351 patent would have been obvious over the combined teachings of Nagai and Jagtiani.

In summary:

| Claims | 35 U.S.C. § | Reference(s) | Claims Shown Unpatentable | Claims Not shown Unpatentable |
|---|---|---|---|---|
| 7–15 | 103 | Nagai, Jagtiani | 7–15 | |
| **Overall Outcome** | | | 7–15 | |

## IV. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has shown by a preponderance of the evidence that claims 7–15 are unpatentable; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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[6] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding*. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

[7] Patent Owner did not introduce any evidence of objective indicia of nonobviousness in this proceeding.

IPR2020-01503
Patent 10,401,351 B2

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US010401351B2

(12) **United States Patent**
**Nagai et al.**

(10) **Patent No.: US 10,401,351 B2**
(45) **Date of Patent: Sep. 3, 2019**

(54) **SAMPLE ANALYZER AND COMPUTER PROGRAM PRODUCT**

(71) Applicant: **SYSMEX CORPORATION**, Kobe-shi, Hyogo (JP)

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(73) Assignees: **Sysmex Corporation**, Kobe (JP); **Sysmex America, Inc.**, Lincolnshire, IL (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/363,694**

(22) Filed: **Mar. 25, 2019**

(65) **Prior Publication Data**

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**Related U.S. Application Data**

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(Continued)

(30) **Foreign Application Priority Data**

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***G01N 15/06*** (2006.01)
***G01N 35/00*** (2006.01)
(Continued)

(52) **U.S. Cl.**
CPC ..... ***G01N 33/5091*** (2013.01); ***G01N 15/12*** (2013.01); ***G01N 15/1459*** (2013.01);
(Continued)

(58) **Field of Classification Search**
CPC ..... G01N 15/06; G01N 35/00; G01N 15/12; G01N 35/5091
(Continued)

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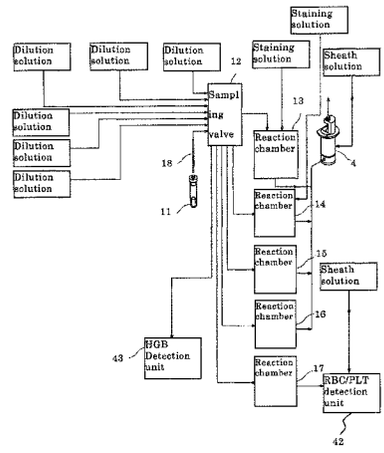
*Primary Examiner* — Brian J. Sines
(74) *Attorney, Agent, or Firm* — Brinks Gilson & Lione

(57) **ABSTRACT**

A sample analyzer prepares a measurement sample from a blood sample or a body fluid sample which differs from the blood sample; measures the prepared measurement sample; obtains characteristic information representing characteristics of the components in the measurement sample; sets either a blood measurement mode for measuring the blood sample, or a body fluid measurement mode for measuring the body fluid sample as an operating mode; and measures the measurement sample prepared from the blood sample by executing operations in the blood measurement mode when the blood measurement mode has been set, and measuring the measurement sample prepared from the body fluid sample by executing operations in the body fluid measurement mode that differs from the operations in the blood
(Continued)



measurement mode when the body fluid measurement mode has been set, is disclosed. A computer program product is also disclosed.

**29 Claims, 17 Drawing Sheets**

**Related U.S. Application Data**

No. 15/908,339, filed on Feb. 28, 2018, now Pat. No. 10,151,746, which is a continuation of application No. 14/594,319, filed on Jan. 13, 2015, now Pat. No. 9,933,414, which is a continuation of application No. 13/891,667, filed on May 10, 2013, now Pat. No. 8,968,661, which is a continuation-in-part of application No. 12/023,830, filed on Jan. 31, 2008, now Pat. No. 8,440,140.

(51) **Int. Cl.**

| | |
|---|---|
| ***G01N 15/12*** | (2006.01) |
| ***G01N 33/50*** | (2006.01) |
| ***G01N 15/14*** | (2006.01) |
| ***G01N 33/72*** | (2006.01) |
| *G01N 15/00* | (2006.01) |

(52) **U.S. Cl.**

CPC ..... ***G01N 33/5094*** (2013.01); ***G01N 33/721*** (2013.01); ***G01N 33/726*** (2013.01); *G01N 2015/008* (2013.01); *G01N 2015/0073* (2013.01); *G01N 2015/0076* (2013.01); *G01N 2015/1486* (2013.01); *Y10T 436/11* (2015.01); *Y10T 436/113332* (2015.01)

(58) **Field of Classification Search**

USPC ..... 422/50, 68.1, 62, 63, 82.01, 82.05; 436/43, 47, 48, 49, 50, 63, 66, 174, 17, 436/178, 180

See application file for complete search history.

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| EP | 0 679 889 | A3 | 3/1996 |
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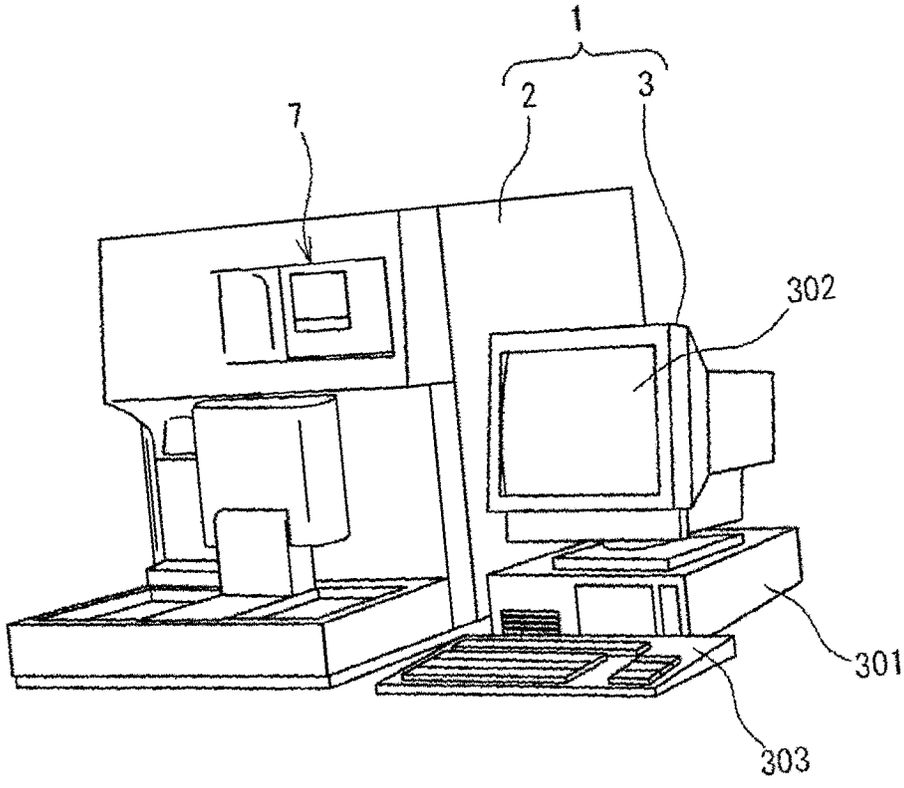



FIG.1

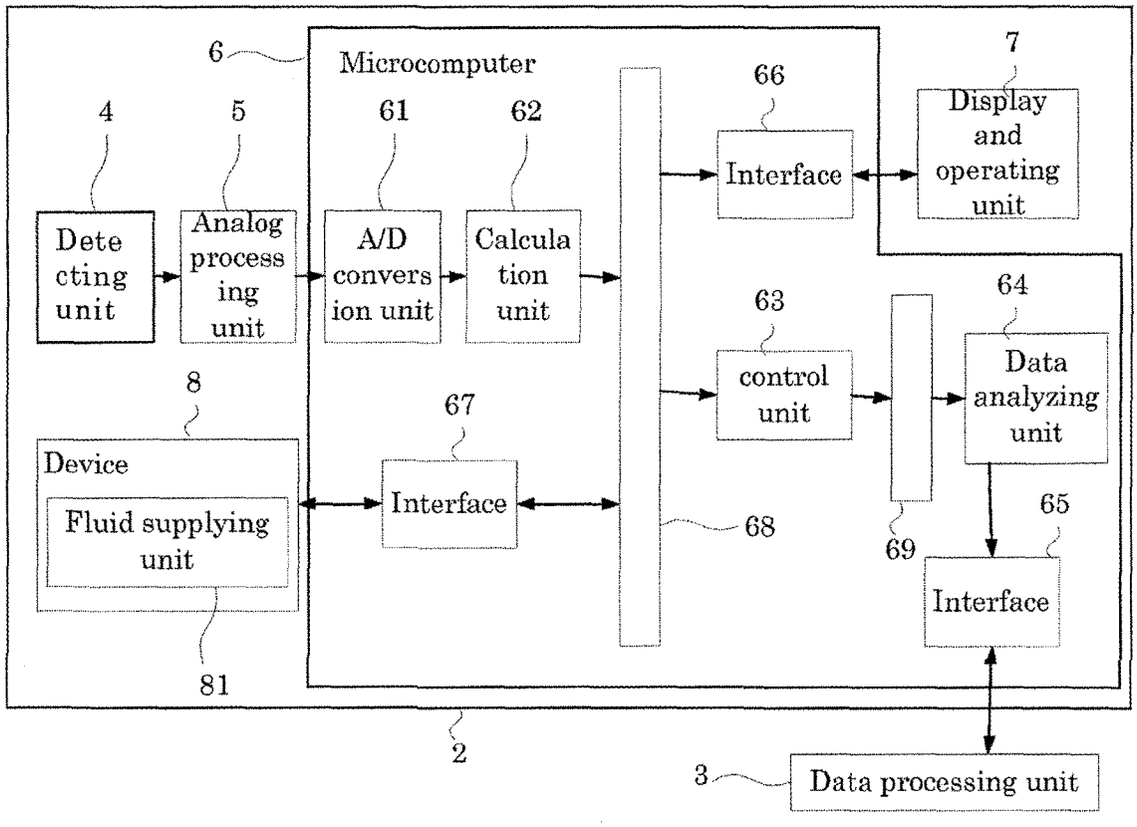

6
Microcomputer
7
66
4
5
61
62
Interface
Display and operating unit
Dete cting unit
Analog process ing unit
A/D convers ion unit
Calcula tion unit
63
64
control unit
Data analyzing unit
8
67
Device
Interface
Fluid supplying unit
68
69
65
Interface
81
2
3
Data processing unit

FIG.2

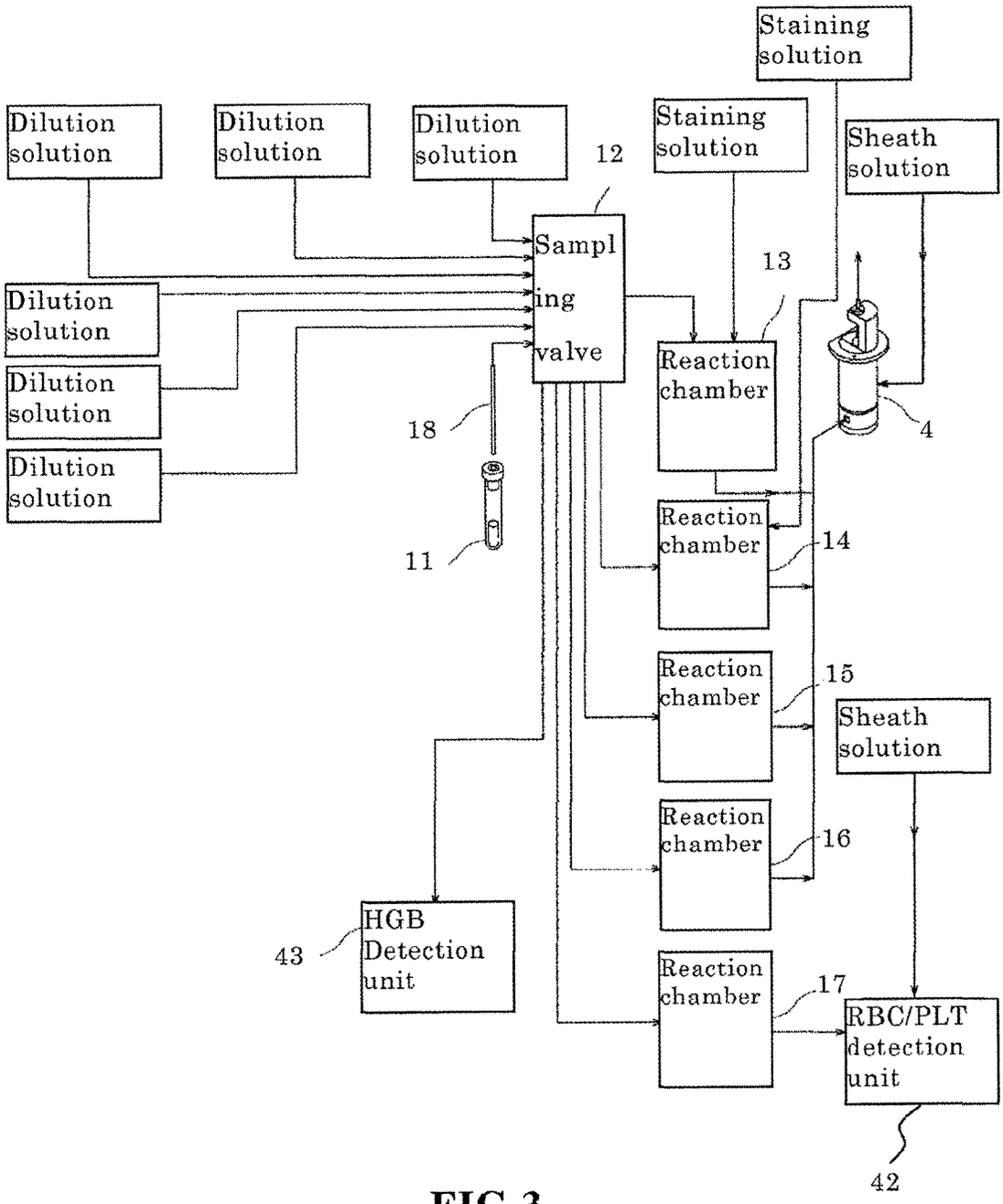

Staining solution
Dilution solution
Dilution solution
Dilution solution
12
Staining solution
Sheath solution
Sampl ing valve
13
Dilution solution
Dilution solution
Dilution solution
Reaction chamber
18
4
11
Reaction chamber
14
Reaction chamber
15
Sheath solution
Reaction chamber
16
43
HGB Detection unit
Reaction chamber
17
RBC/PLT detection unit
42

FIG.3

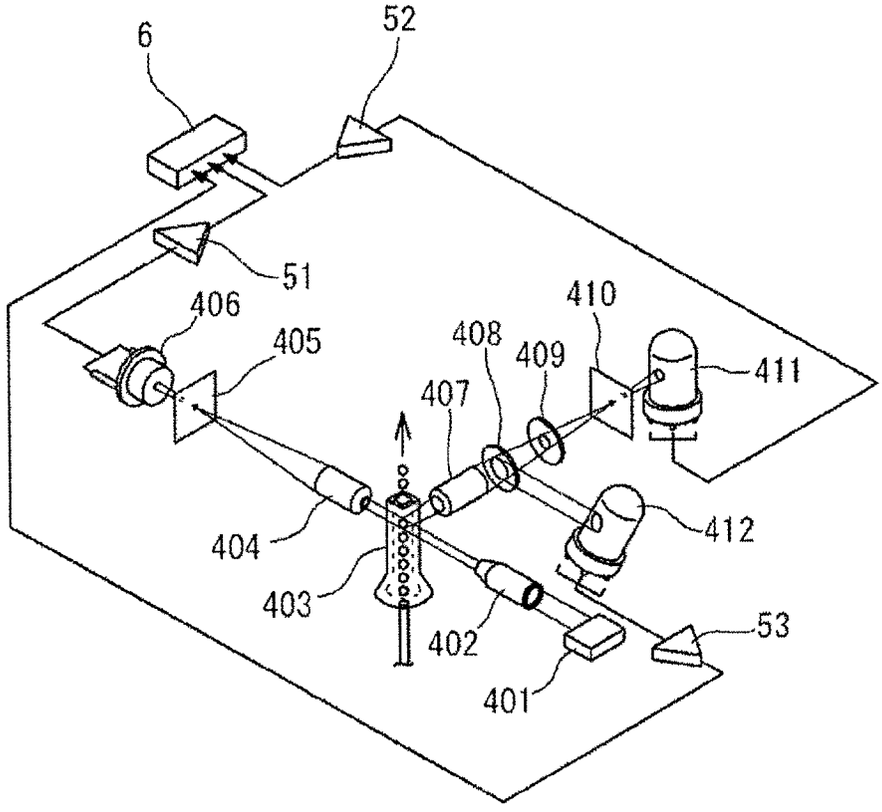



FIG.4

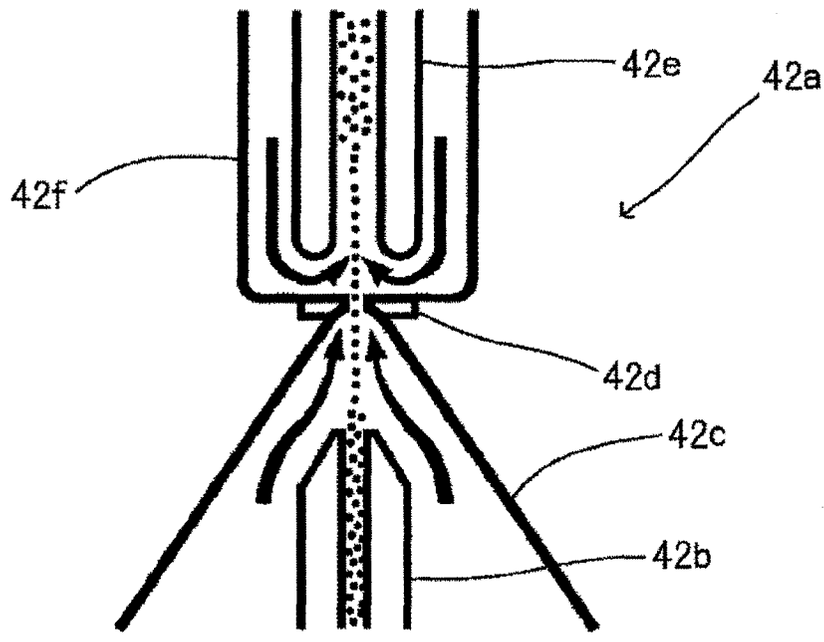



FIG.5

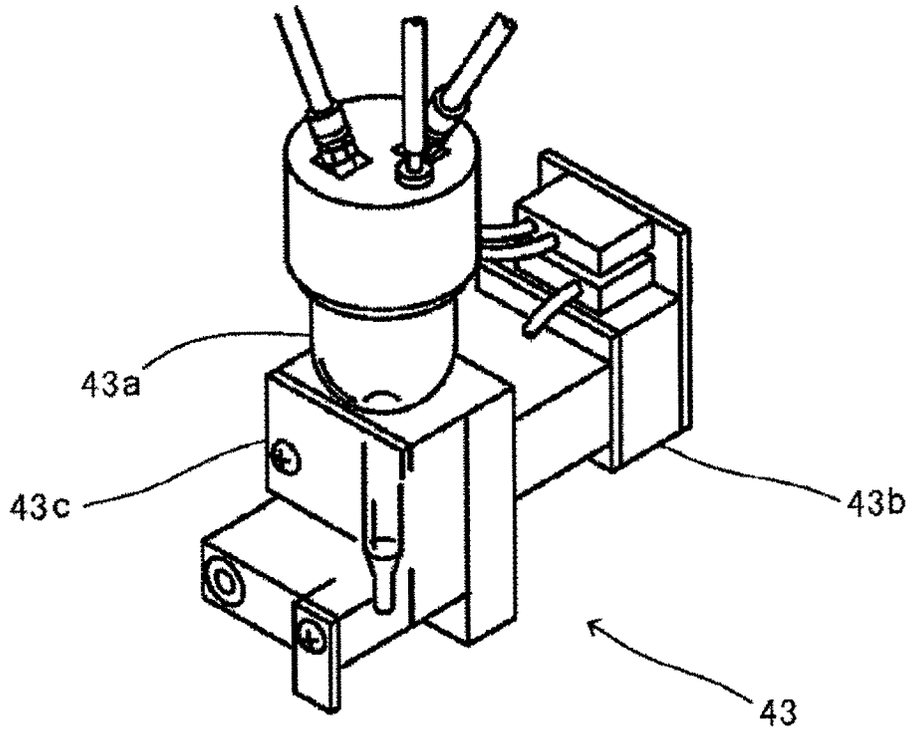



FIG.6

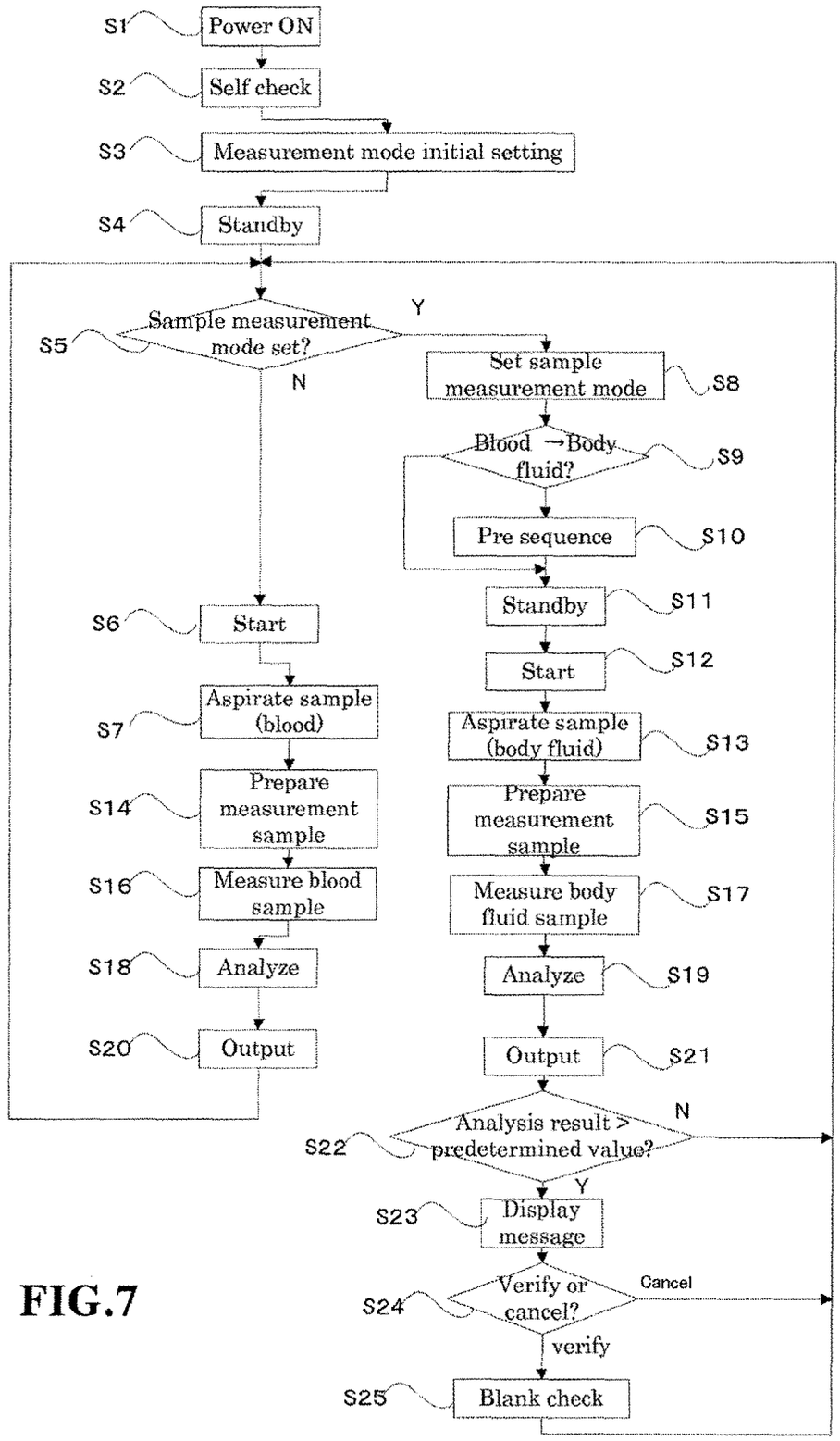
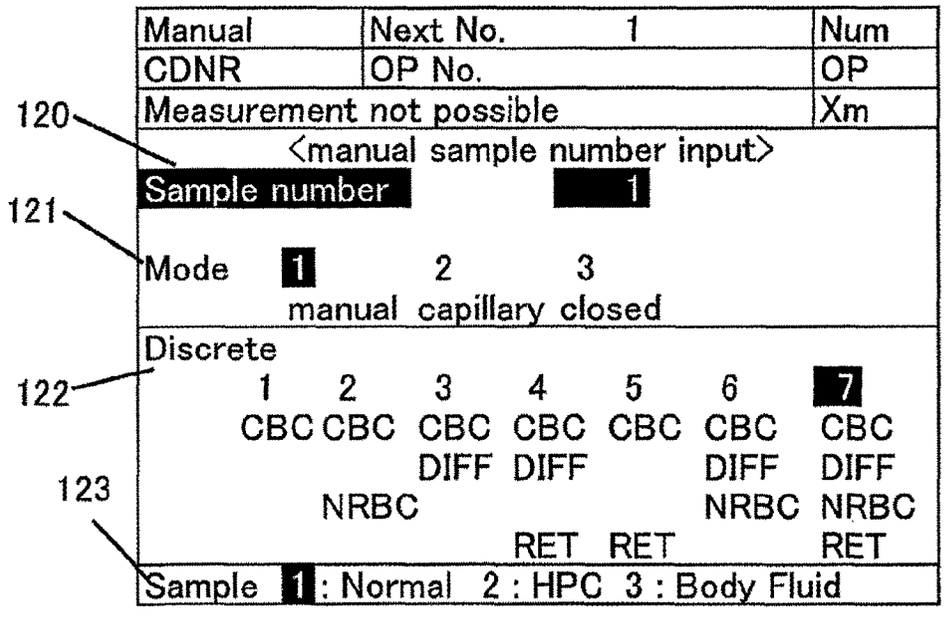



FIG.7

Beckman Coulter Ex. 1001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Next No. 1
Num
CDNR
OP No.
OP
Measurement not possible
Xm
<manual sample number input>
Sample number
1
Mode
1
2
3
manual
capillary
closed
Discrete
1 2 3 4 5 6 7
CBC CBC CBC CBC CBC CBC CBC
DIFF DIFF DIFF DIFF
NRBC NRBC NRBC
RET RET RET
Sample
1 : Normal 2 : HPC 3 : Body Fluid
120
121
122
123

Fig.8

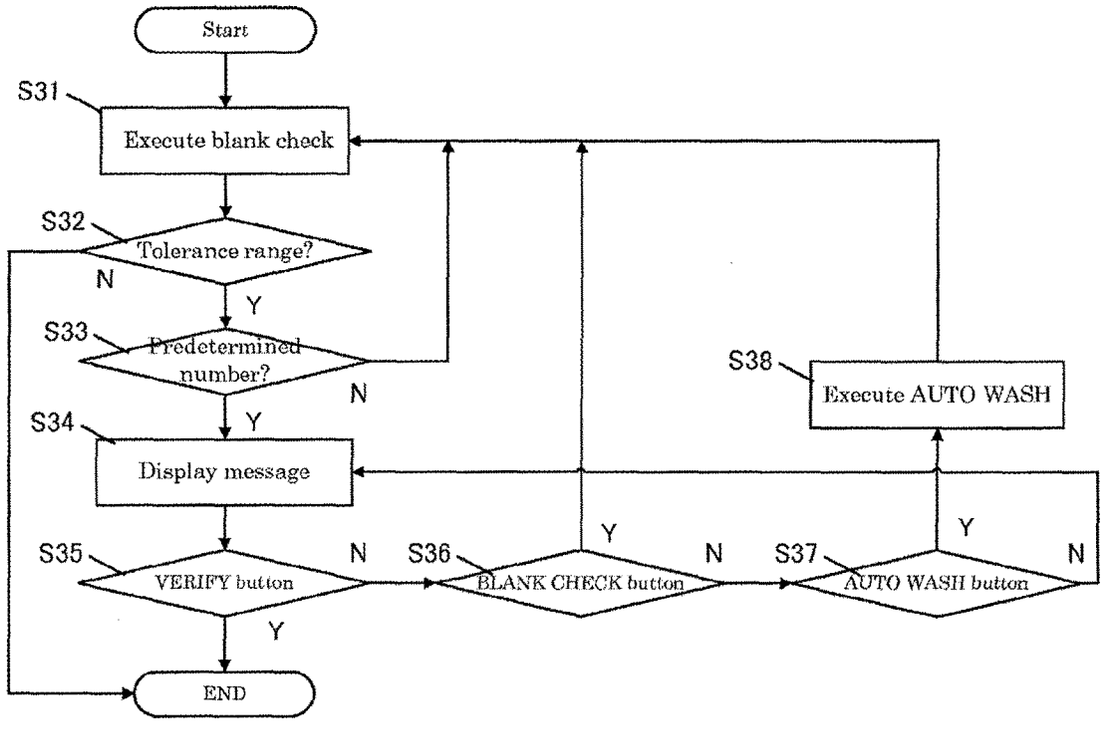

Start
S31
Execute blank check
S32
Tolerance range?
N
Y
S33
Predetermined number?
N
Y
S34
Display message
S35
VERIFY button
N
Y
S36
BLANK CHECK button
N
Y
S37
AUTO WASH button
N
Y
S38
Execute AUTO WASH
END

FIG.9

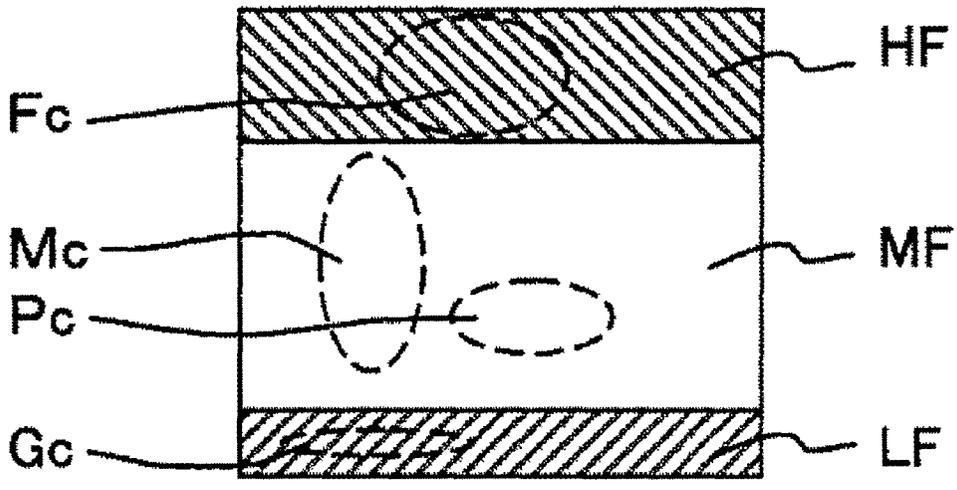
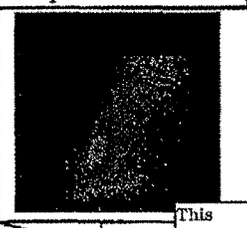



FIG.10

Example 1

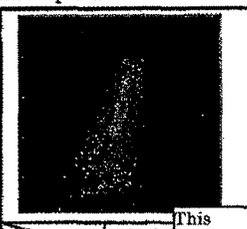
| | Ref | This Method |
|---|---|---|
| WBC | 4580 | 4364 |
| Others | 1420 | 1387 |

Example 2



| | Ref | This Method |
|---|---|---|
| WBC | 1370 | 1160 |
| Others | 670 | 535 |

Example 3



| | Ref | This Method |
|---|---|---|
| WBC | 1360 | 1391 |
| Others | 70 | 74 |

FIG.11

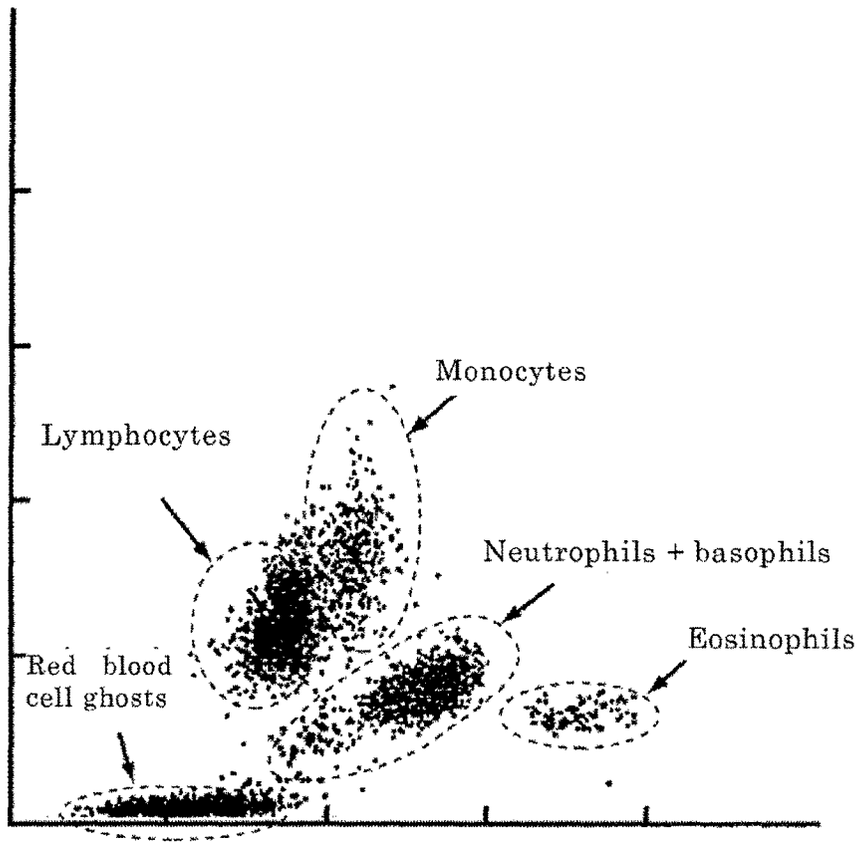

Monocytes
Lymphocytes
Neutrophils + basophils
Eosinophils
Red blood cell ghosts

FIG.12

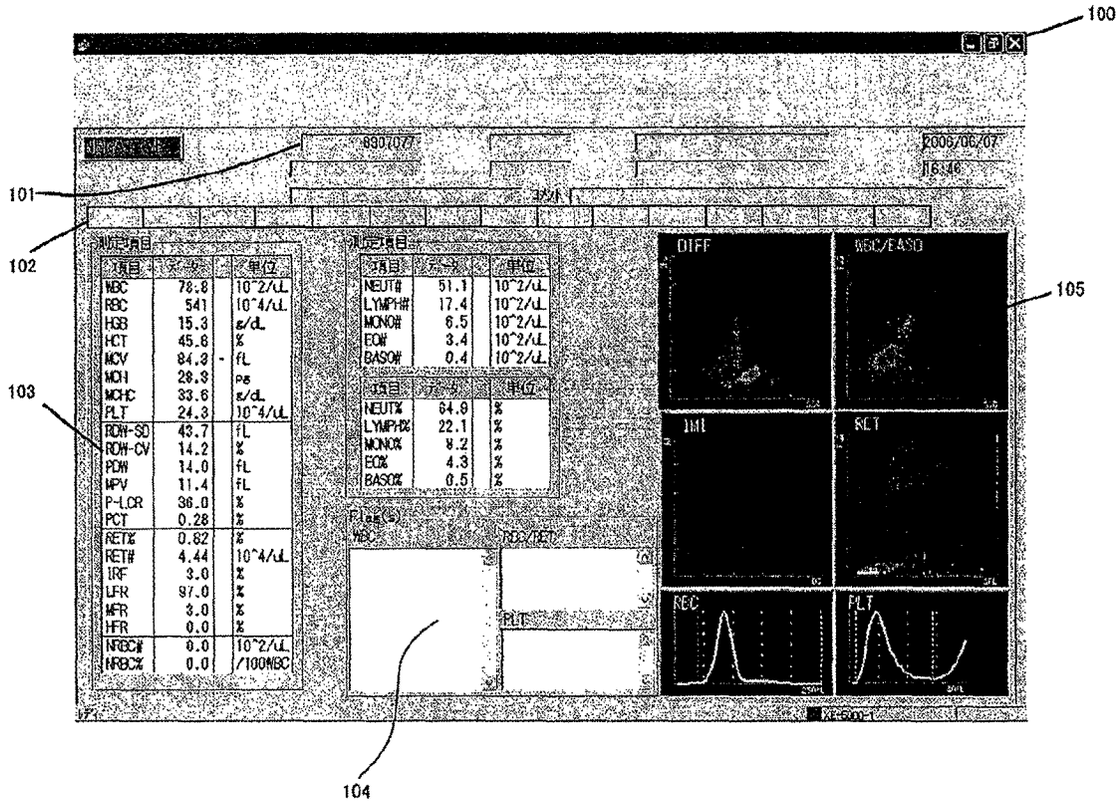



Fig.13

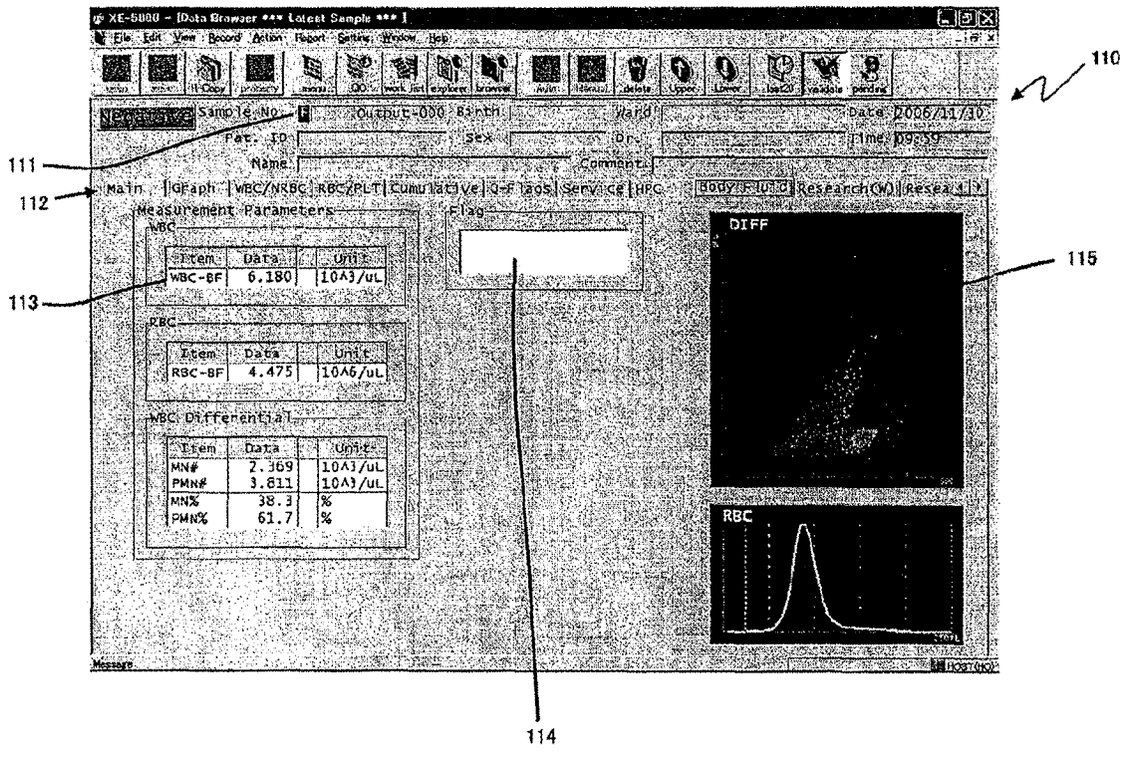

110
111
112
113
114
115
Measurement Parameters
WBC
RBC
WBC Differential
Flag
DIFF
RBC

Fig.14

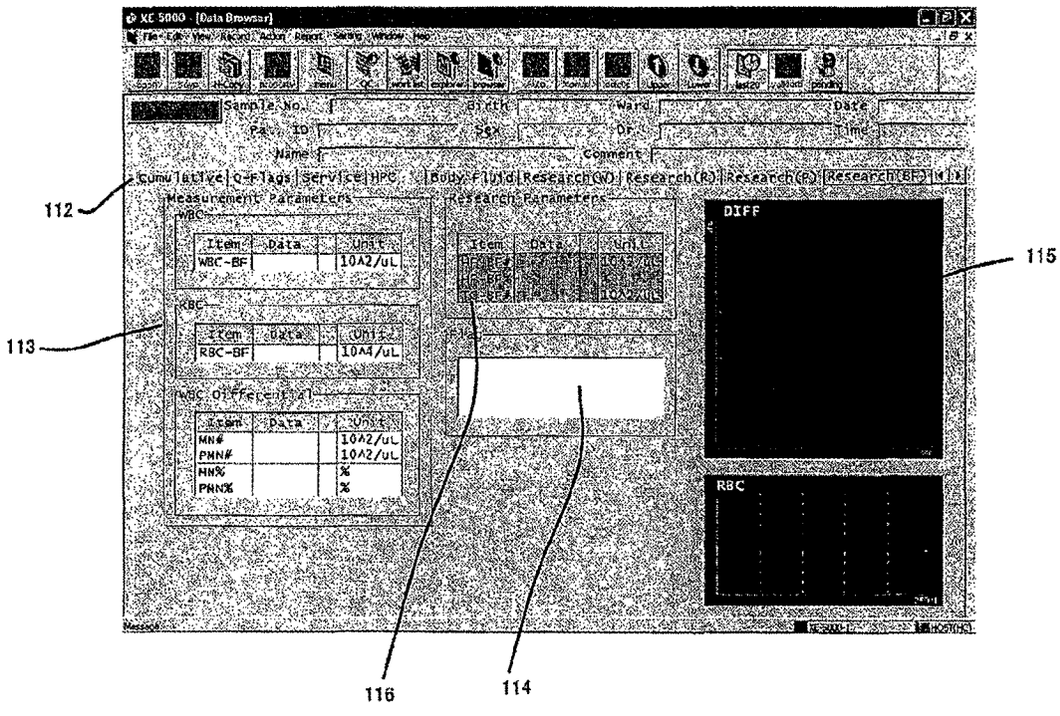

XC 5000 - [Data Browser]
Sample No.
Birth
Ward
Date
Name
Comment
Cumulative
Q-Flags
Service
HPC
Body Fluid
Research(W)
Research(R)
Research(P)
Research(BF)
Measurement Parameters
WBC
Item
Data
Unit
WBC-BF
10A2/uL
RBC
RBC-BF
10A4/uL
WBC Differential
MN#
PMN#
MN%
PMN%
Research Parameters
DIFF
RBC
112
113
115
116
114

Fig.15

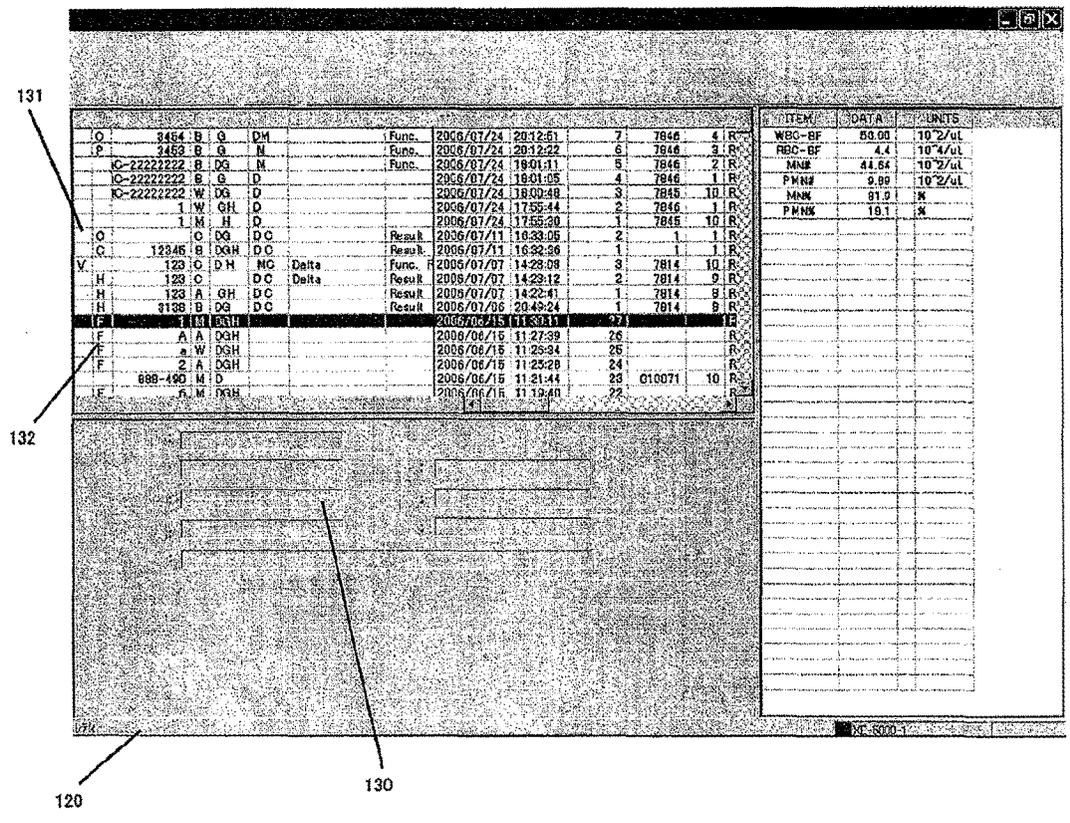



Fig.16

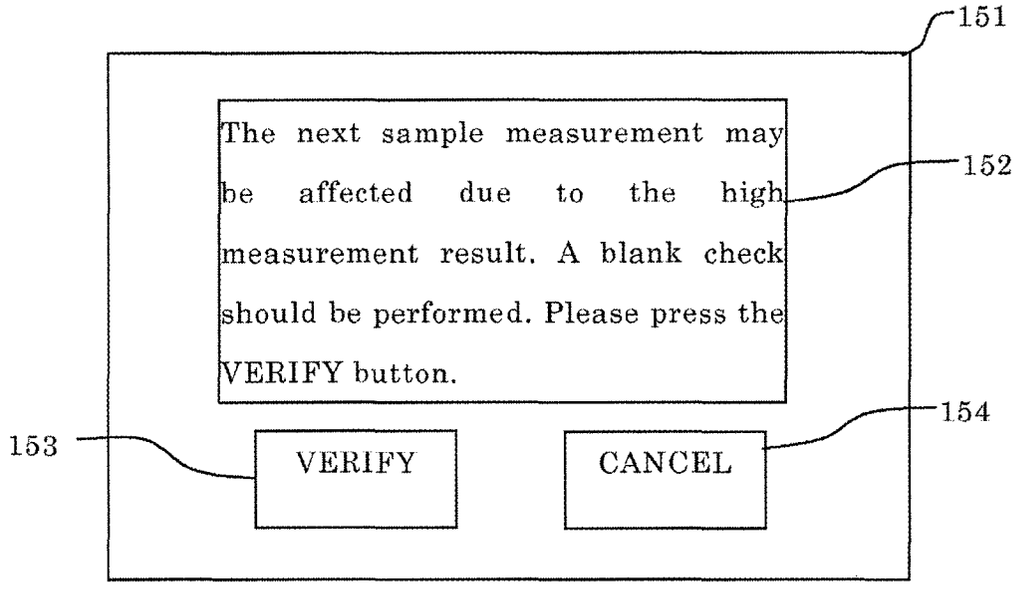

151
The next sample measurement may be affected due to the high measurement result. A blank check should be performed. Please press the VERIFY button.
152
153
VERIFY
CANCEL
154

FIG.17

# SAMPLE ANALYZER AND COMPUTER PROGRAM PRODUCT

This application is a continuation of U.S. application Ser. No. 16/214,417 filed Dec. 10, 2018, which is a continuation of U.S. application Ser. No. 15/908,339 filed Feb. 28, 2018, which is a continuation of U.S. application Ser. No. 14/595,319 filed Jan. 13, 2015, now U.S. Pat. No. 9,933,414, which is a continuation of U.S. application Ser. No. 13/891,667 filed May 10, 2013, now U.S. Pat. No. 8,968,661, which is a continuation of U.S. application Ser. No. 12/023,830 filed Jan. 31, 2008, now U.S. Pat. No. 8,440,140, claiming priority to Japanese Application No. 2007-022523 filed on Feb. 1, 2007 and to Japanese Application No. 2007-095226 filed on Mar. 30, 2007, all of which are incorporated herein by reference in their entireties.

## FIELD OF THE INVENTION

The present invention relates to a sample analyzer and a computer program product capable of measuring not only blood, but also body fluids other than blood such as cerebrospinal fluid (spinal fluid), fluid of the thoracic cavity (pleural fluid), abdominal fluid and the like.

## BACKGROUND

In the field of clinical examinations, blood is routinely collected from a body and used as a sample which is measured by a sample analyzer to aid diagnosis and monitor treatment. Furthermore, body fluids other than blood are also often used as samples which are measured by a sample analyzer. The body fluids are usually transparent and contain very few cells, however, cells such as bacteria, abnormal cells, and hemorrhage (blood cells) and the like may be found in cases of disease, tumors of related organs, and injury.

When cerebrospinal fluid, which is one type of body fluid, is measured, for example, it is possible to make the following estimations from the measurement results.

Increase of red blood cells: subarachnoidal hemorrhage

Increase of neutrophils: meningitis

Increase of eosinophils: infectious disease (parasites and fungus)

Increase of monocytes: tuberculosis meningitis, viral meningitis

Other cells: advanced meningeal tumor

Japanese Laid-Open Patent Publication No. 2003-344393 discloses a blood cell analyzer which is capable of measuring cells in a body fluid. In Japanese Laid-Open Patent Publication No. 2003-344393, an operator prepares a measurement sample prior to performing the measurements by mixing a fluid sample and reagent (aldehyde, surface active agent, and cyclodextrin) in order to stably store the body fluid for a long period, and this measurement sample is later subjected to fluid analysis by the sample analyzer.

In the art of Japanese Laid-Open Patent Publication No. 2003-344393, however, the measurement sample is not prepared by the sample analyzer when the body fluid is measured, rather the measurement sample must be prepared by the operator of the analyzer. Furthermore, the sample analyzer disclosed in Japanese Laid-Open Patent Publication No. 2003-344393 does not disclose measurement operations suited to the fluid when measuring a body fluid.

## SUMMARY OF THE INVENTION

The scope of the present invention is defined solely by the appended claims, and is not affected to any degree by the statements within this summary.



A first aspect of the present invention is a sample analyzer comprising: a measuring part for preparing a measurement sample from a blood sample or a body fluid sample that differs from the blood sample, measuring the prepared measurement sample, and obtaining characteristic information representing characteristics of components within the measurement sample; a mode setting means for setting either a blood measurement mode for measuring the blood sample, or a body fluid measurement mode for measuring the body fluid sample as an operating mode; a first control means for controlling the measuring part so as to execute operations in the blood measurement mode when the blood measurement mode has been set by the mode setting means; and a second control means for controlling the measuring part so as to execute operations in the body fluid measurement mode which differs from the operations in the blood measurement mode when the body fluid measurement mode has been set by the mode setting means.

A second aspect of the present invention is a sample analyzer comprising: a measuring part for preparing a measurement sample from a blood sample or a body fluid sample that differs from the blood sample, measuring the prepared measurement sample, and obtaining characteristic information representing characteristics of components within the measurement sample; a mode setting means for setting either a blood measurement mode for measuring the blood sample, or a body fluid measurement mode for measuring the body fluid sample as an operating mode; a first analyzing means for executing a first analysis process based on the characteristic information obtained by measuring the measurement sample prepared by the measuring part from the blood sample when the blood measurement mode has been set by the mode setting means; and a second analyzing means for executing a second analysis process which differs from the first analysis process based on the characteristic information obtained by measuring the measurement sample prepared by the measuring part from the body fluid sample when the body fluid measurement mode has been set by the mode setting means.

A third aspect of the present invention is a sample analyzer comprising: a measuring part for preparing a measurement sample from a blood sample or a body fluid sample that differs from the blood sample, measuring the prepared measurement sample, and obtaining characteristic information representing characteristics of components within the measurement sample; a mode switching means for switching an operating mode from a blood measurement mode for measuring the blood sample to a body fluid measurement mode for measuring the body fluid sample; and a blank measurement controlling means for controlling the measuring part so as to measure a blank sample that contains neither the blood sample nor the body fluid sample when the mode switching means has switched the operating mode from the blood measurement mode to the body fluid measurement mode.

A fourth aspect of the present invention is a computer program product, comprising: a computer readable medium; and instructions, on the computer readable medium, adapted to enable a general purpose computer to perform operations, comprising: a step of preparing a measurement sample from a blood sample or a body fluid sample which differs from the blood sample; a step of measuring the prepared measurement sample; a step of obtaining characteristic information representing characteristics of the components in the measurement sample; a step of setting either a blood measurement mode for measuring the blood sample, or a body fluid measurement mode for measuring the body fluid sample as

an operating mode; and a step of measuring the measurement sample prepared from the blood sample by executing operations in the blood measurement mode when the blood measurement mode has been set, and measuring the measurement sample prepared from the body fluid sample by executing operations in the body fluid measurement mode that differs from the operations in the blood measurement mode when the body fluid measurement mode has been set.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an exterior view of a blood cell analyzer of a first embodiment of the present invention;

FIG. **2** is a block diagram of the measuring unit of the analyzer;

FIG. **3** is a block diagram of the fluid supplying unit;

FIG. **4** shows the optical system of the white blood cell detection unit;

FIG. **5** shows the RBC/PLT detection unit;

FIG. **6** shows the HGB detection unit;

FIG. **7** is a flow chart of the sample measuring process;

FIG. **8** shows the display screen for setting the measurement mode;

FIG. **9** is a flow chart showing the pre sequence process;

FIG. **10** is a schematic view of a scattergram derived from measurements of a DIFF measurement sample prepared from body fluid;

FIG. **11** compares measurement results by the blood cell analyzer of the embodiment and measurement results by a reference method;

FIG. **12** is a schematic view of a scattergram derived from measurements of a DIFF measurement sample prepared from blood;

FIG. **13** is a display screen showing the measurement results in the blood measurement mode;

FIG. **14** is a display screen showing the measurement results in the body fluid measurement mode;

FIG. **15** is a display screen showing the measurement results in the body fluid measurement mode;

FIG. **16** is a display screen showing the measurement results in the body fluid measurement mode; and

FIG. **17** is a confirmation screen at the start of the blank check which is displayed in the body fluid measurement mode.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred embodiments of the present invention will be described hereinafter with reference to the drawings.

FIG. **1** shows a sample analyzer **1**. The sample analyzer **1** is configured as an automatic multi-item blood cell analyzer which performs blood analysis by measuring blood samples held in sample containers (blood collection tubes), obtaining characteristics information representing the characteristics of the blood cells contained in the sample, and analyzing the characteristic information. The sample analyzer **1** is also capable of analyzing body fluids. In the blood cell analyzer of the present embodiment, the body fluids used as analysis objects include, fluid within the body cavity other than blood. Specifically, cerebrospinal fluid (spinal fluid, CSF: fluid filling the ventricle or sublemmal cavity), fluid of the thoracic cavity (pleural fluid, PE: fluid collected in pleural cavity), abdominal fluid (fluid collected in the abdominal cavity), fluid of the cardiac sac (fluid collected in the cardiac sac), synovial fluid (fluid present in joints, synovial sac, peritenon) and the like. Among types of body fluid which can be analyzed are dialysate of peritoneal dialysis (CAPD), intraperitoneal rinse and the like. Cells are usually not observed in these body fluids, however, the fluids may contain blood cells, abnormal cells, and cells such as bacteria in the case of disease, tumor of related organs, or injury. For example, it is possible to clinically estimate the following from measurement results in the case of cerebrospinal fluid. For example, sub-arachnoidal hemorrhage is indicted when there is an increase of red blood cells, meningitis is indicated when there is an increase of neutrophils, infectious disease (parasitic and fungal) is indicated when there is an increase of eosinophils, tuberculosis meningitis and viral meningitis are indicated when there is an increase of monocytes, and advanced meningeal tumor is indicated when there is an increase of other cells. ed In the case of abdominal and thoracic fluids, cancers may be indicated when analysis of finds nucleated cells other than blood cells, that is, the fluid contains nucleated cells of mesothelial cells, macrophages, tumor cells and the like.



The sample analyzer **1** is provided with a measuring unit **2** which has the function of measuring blood and body fluid samples, and a data processing unit **3** which obtains analysis results by processing the measurement results output from the measurement unit **2**. The data processing unit **3** is provided with a control unit **301**, a display unit **302**, and an input unit **303**. Although the measuring unit **2** and data processing unit **3** are separate devices in FIG. **1**, the both may also be integrated in a single apparatus.

FIG. **2** is a block diagram of the measuring unit **2** of the analyzer **1**. As shown in FIG. **2**, the measuring unit **2** is provided with a blood cell detecting unit **4**, an analog processing unit **5** which processes the output (analog signals) of the detecting unit **4**, microcomputer unit **6**, display and operating unit **7**, and a device **8** for measuring blood and body fluids. The device **8** includes a fluid supplying unit **81** which is described below.

FIG. **3** is a block diagram showing the structure of the fluid supplying unit **81**. As shown in FIG. **3**, the fluid supplying unit **81** is provided with a sample aspiration nozzle **18**, a plurality of reagent containers, a sampling valve **12**, and reactions chambers **13** through **17**. The sample aspiration nozzle **18** aspirates sample from a sample container, and delivers the sample to the sampling valve **12**. The sampling valve **12** divides the delivered sample into several aliquots of predetermined volume. The number of divisions differs depending on the mode of measurement (discrete mode); in the CBC mode the sample is divided into three aliquots to measure the number of red blood cells, the number of white blood cells, the number of platelets, and the hemoglobin concentration. In addition to the CBC measurement items, the sample is divided into four aliquots in the CBC−DIFF mode so as to also classify five types of white blood cells. Furthermore, In addition to the measurement items of the CBC+DIFF mode, the sample is divided into five aliquots in the CBC+DIFF+RET mode so as to also measure reticulocytes.

Similarly, in addition to the measurement items of the CBC+DIFF mode, the sample is divided into five aliquots in the CBC+DIFF+NRBC mode so as to also measure nucleated red blood cells. In addition to the measurement items of the CBC+DIFF+RET mode, the sample is divided into six aliquots in the CBC+DIFF+RET+NRBC mode so as to also measure nucleated red blood cells. The above mentioned measurement modes are blood measuring modes which measure whole blood. Finally, the sample is divided into two aliquots in the body fluid measuring mode for measuring body fluid.

Reagent (dilution solution) is introduced from a reagent container to the sampling valve, and the aliquots of the divided sample are delivered together with the reagent to the reaction chambers **13** through **17** and an HGB detection unit **43**, which is described later. a predetermined amount of sample (aliquot) and a predetermined amount of reagent and a predetermined amount of stain collected by the sampling valve **12** are supplied to the reaction chamber **13** by a dosage pump which is not shown in the drawing, the sample and reagent are mixed to prepare a measurement sample for four classifications of white blood cells (DIFF).

The reagent "stomatolyzer 4DL" made by Sysmex Corporation may be used as the dilution solution. This reagent contains surface active agent and induces hemolysis of red blood cells. The reagent "stomatolyzer 4DS" made by Sysmex Corporation may be used as the stain. This stain contains ethylene glycol, low molecular alcohol, and polymethene colorant; a 50× dilute sample is ultimately prepared by staining the blood cell component after hemolysis by the dilution agent.

When the body fluid measurement mode has been selected, a measurement sample for the classification of white blood cells is prepared from a fluid sample under the conditions of the amount of the sample and reagent used for the four classifications of white blood cells are identical, the reagents are identical, and the amounts of the reagent are identical. In the white blood cell classification of the body fluid measurement mode, the white blood cells are classified, not in four types, but two types, as shall be described later.

A predetermined amount of sample collected by the sampling valve **12**, a predetermined amount of hemolytic dilution agent, and a predetermined amount of stain solution are supplied to the reaction chamber **14** by a dosage pump which is not shown in the drawing, the sample and reagents are then mixed to prepare a measurement sample for measuring nucleated red blood cells (NRBC).

A predetermined amount of sample collected by the sampling valve **12**, a predetermined amount of dilution agent, and a predetermined amount of stain solution are supplied to the reaction chamber **15** by a dosage pump which is not shown in the drawing, the sample and reagents are then mixed to prepare a measurement sample for measuring reticulocytes (RET).

A predetermined amount of sample collected by the sampling valve **12**, and a predetermined amount of hemolytic dilution agent are supplied to the reaction chamber **16** by a dosage pump which is not shown in the drawing, the sample and reagents are then mixed to prepare a measurement sample for measuring white blood cells and basophils (WBC/BASO).

A predetermined amount of sample collected by the sampling valve **12**, and a predetermined amount of dilution solution are supplied to the reaction chamber **17** by a dosage pump which is not shown in the drawing, the sample and reagents are then mixed to prepare a measurement sample for measuring red blood cells and platelets (RBC/PLT).

A predetermined amount of sample collected by the sampling valve **12**, and a predetermined amount of hemolytic dilution agent are supplied to the HGB detection unit **43** which is described later.

The detection device **4** is provided with a white blood cell detection unit **41** for detecting white blood cells. The white blood cell detection unit **41** is also used to detect nucleated red blood cells and reticulocytes. In addition to the white blood cell detection unit, the detection device **4** is also provided with an RBC/PLT detection unit **42** for measuring the number of red blood cells and the number of platelets, and an HGB detection unit **43** for measuring the amount of pigment in the blood.



The white blood cell detection unit **41** is configured as an optical detection unit, specifically, a detection unit which uses a flow cytometric method. Cytometry measures the optical properties and physical properties of cells and other biological particles, and flow cytometry measures these particles as they pass by in a narrow flow. FIG. **4** shows the optical system of the white blood cell detection unit **41**. In the same drawing, the beam emitted from a laser diode **401** irradiates, via a collimator lens **402**, the blood cells passing through the interior of a sheath flow cell **403**. The intensity of the front scattered light, the intensity of the side scattered light, and the intensity of the side fluorescent light from the blood cells within the sheath flow cell irradiated by the light are detected by the white blood cell detection unit **41**.

The scattered light is a phenomenon due to the change in the direction of travel of the light caused by particles such as blood cells and the like which are present as obstructions in the direction of travel of the light. Information on the characteristics of the particles related to the size and composition of the particles can be obtained by detecting this scattered light. The front scattered light emerges from the particles in approximately the same direction as the direction of travel of the irradiating light. Characteristic information related to the size of the particle (blood cell) can be obtained from the front scattered light. The side scattered light emerges from the particle in an approximate perpendicular direction relative to the direction of travel of the irradiating light. Characteristic information related to the interior of the particle can be obtained from the side scattered light. When a particle is irradiated by laser light, the side scattered light intensity is dependent on the complexity (that is, nucleus shape, size, density, and granularity) of the interior of the cell. therefore, the blood cells can be classified (discriminated) and the number of cells can be counted by using the characteristics of the side scattered light intensity. Although the front scattered light and side scattered light are described as the scattered light used in the present embodiment, the present invention is not limited to this configuration inasmuch as scattered light of any angle may also be used relative to the optical axis of the light emitted from a light source that passes through the sheath flow cell insofar as scattered light signals are obtained which represent the characteristics of the particles necessary for analysis.

When fluorescent material such as a stained blood cell is irradiated by light, light is given off by the particle at a wavelength which is longer than the wavelength of the irradiating light. The intensity of the fluorescent light is increased by the stain, and characteristics information can be obtained relating to the degree of staining of the blood cell by measuring the fluorescent light intensity. The classification and other measurements of the white blood cells can then be performed by the difference in the (side) fluorescent light intensity.

As shown in FIG. **4**, the front scattered light from the blood cell (white blood cells and nucleated red blood cells) which pass through the sheath flow cell **403** is received by a photodiode (front scattered light receiving unit) **406** through a collective lens **404** and pinhole **405**. The side scattered light is received by a photo multiplexer (side scattered light receiving unit) **411** through a collective lens **407**, dichroic mirror **408**, optical filter **409**, and pinhole **410**. The side fluorescent light is received by a photo multiplexer (side fluorescent light receiving unit) **412** through the collective lens **407** and dichroic mirror **408**. The photoreception

signals output from the light receiving units **406**, **411**, and **412** are subjected to analog processing such as amplification and waveform processing and the like by an analog processing unit **5** which is configured by amps **51**, **52**, **53** and the like, and the analog-processed photoreception signals are provided to the microcomputer **6**.

The configuration of the RBC/PLT detection unit **42** is described below. FIG. **5** is a schematic view briefly showing the structure of the RBC/PLT detection unit **42**. The RBC/PLT detection unit **42** is capable of measuring the numbers of red blood cells and platelets by a sheath flow-DC detection method. The RBC/PLT detection unit **42** has a sheath flow cell **42***a* as shown in FIG. **5**. The sheath flow cell **42***a* is provided with a sample nozzle **42***b* which is open toward the top so that sample can be supplied from the reaction chamber **17** to the sample nozzle **42***b*. The sheath flow cell **42***a* has a tapered chamber **42***c* which narrows toward the top, and the sample nozzle **42***b* is disposed in the center part within the chamber **42***c*. An aperture **42***d* is provided at the top end of the chamber **42***c*, and this aperture **42***d* is aligned with the center position of the sample nozzle **42***b*. Measurement sample supplied from the sample supplying unit is sent upward from the tip of the sample nozzle **42***b*, and front sheath fluid is simultaneously supplied to the chamber **42***c* and flows upward toward the aperture **42***d*. The flow of the measurement sample, which is encapsulated in the front sheath fluid, is narrowly constricted by the tapered chamber **42***c* and the blood cells within the measurement sample pass one by one through the aperture **42***d*. Electrodes are provided at the aperture **42***d*, and a direct current is supplied between these electrodes. The change in the resistance of the direct current is detected at the aperture **42***d* when the measurement sample flows through the aperture **42***d*, and the electrical signal of the change in resistance is output to the controller **25**. Since the resistance of the direct current increases when blood cells pass through the aperture **42***d*, the electrical signals reflect information of the passage of the blood cells through the aperture **42***d* so that the numbers of red blood cells and platelets can be counted by subjecting these electrical signals to signal processing.

A recovery tube **42***e*, which extends vertically, is provided above the aperture **42***d*. The recovery tube **42***e* is disposed within a chamber **42***f* which is connected to the chamber **42***c* through the aperture **42***d*. The inner wall of the chamber **42***f* is separated from the bottom end of the recovery tube **42***e*. The chamber **42***f* is configured to supply a back sheath, and this back sheath flows downward through the chamber **42***f* in a region outside the recovery tube **42***e*. The back sheath which flows outside the recovery tube **42***e* arrives at the bottom part of the chamber **42***f*, and thereafter flows between the inner wall of the chamber **42***f* and the bottom end of the recovery tube **42***e* so as to flow into the interior of the recovery tube **42***e*. The blood cells which has passed through the aperture **42***d* are therefore prevented from refluxing, thus preventing erroneous detection of the blood cells.

The configuration of the HGB detection unit **43** is described below. The HGB detection unit **43** is capable of measuring the amount of hemoglobin (HGB) by an SLS hemoglobin method. FIG. **6** is a perspective view of the structure of the HGB detection unit **43**. The HGB detection unit **43** has a cell **43***a* for accommodating a diluted sample, a light-emitting diode **43***b* for emitting light toward the cell **43***a*, and a photoreceptor element **43***c* for receiving the transmission light that has passed through the cell **43***a*. A fixed amount of blood is diluted with dilution fluid and a predetermined hemolytic agent at a predetermined dilution ratio by the sampling valve **12** to prepare a dilute sample. The hemolytic agent has properties which transform the hemoglobin in the blood to SLS-hemoglobin. The dilute sample is supplied to the cell **43***a* and accommodated therein. In this condition, the light-emitting diode **43***b* emits light that passes through the cell **43***a* and is received by the photoreceptor element **43***c* which is disposed opposite the light-emitting diode **43***b* with the cell **43***a* interposed therebetween. Since the light-emitting diode **43***b* emits light having a wavelength that is highly absorbed by the SLS-hemoglobin, and the cell **43***a* is configured of plastic material which has a high light transmittancy, the photoreceptor element **43***c* only receives the transmission light absorbed by the dilute sample of the light emitted from the light-emitting diode **43***b*. The photoreceptor element **43***c* outputs electrical signals which correspond to the amount of received light (optical density) to the microcomputer **6**, and the microcomputer **6** compares the optical density with the optical density of the dilution solution which was measured previously, then calculates the hemoglobin value.

The microcomputer **6** is provided with an A/D converter **61** for converting the analog signals received from the analog processing unit **5** to digital signals. The output of the A/D converter **61** is sent to a calculation unit **62** of the microcomputer **6**, and calculations are performed for predetermined processing of the photoreception signals in the calculation unit **62**. The calculation unit **62** prepares distribution data (two-dimensional scattergrams (unclassified) and unidimensional histograms) based on the output of the detection device **4**.

The microcomputer **6** is provided with a controller **63** configured by a memory for the control processor and the operation of the control processor, and a data analyzing unit **64** configured by a memory for the analysis processor and the operation of the analysis processor. The controller **63** controls the device **8** configured by a sampler (not shown in the drawing) for automatically supplying blood collection tubes, and a fluid system and the like for preparing and measuring samples, as well as performing other controls. The data analyzing unit **64** executes analysis processing such as clustering and the like on the distribution data. The analysis results are sent to an external data processing device **3** through an interface **65**, and the data processing device **3** processes the data for screen display, storage and the like.

The microcomputer **6** is further provided with an interface **66** which is interposed between the microcomputer **6** and the display and operating unit **7**, and an interface **67** which is interposed between the microcomputer **6** and the device **8**. The calculation unit **62**, controller **63**, and interfaces **66** and **67** are connected through a bus **68**, and the controller **63** and the data analyzing unit **64** are connected through a bus **69**. The display and operating unit **7** includes a start switch by which the operator specifies to start a measurement, and a touch panel type liquid crystal display for displaying various types of setting values and analysis results, and receiving input from the operator.

The operation of the sample analyzer **1** of the present embodiment is described below. FIG. **7** is a flow chart showing the flow of the operation of the sample analyzer of the present embodiment. The sample analyzer **1** starts when a user turns on the power source of the sample analyzer **1** (step S**1**). The sample analyzer **1** first executes a self check during startup (step S**2**). In the self check, the microcomputer **6** tests and checks the operation of all operating device of the sample analyzer **1**, and performs a blank check operation which measures a blank sample that does not contain a real sample. Next, the microcomputer **6** sets an initial measurement mode (step S**3**). The CBC+DIFF mode

is the initial setting. Specifically, in the process of step S3, parameters (operating conditions) for performing blood measurements are set, for example, which reaction chamber to use and the set time for the measurement. The blood measurement mode is thus set as the initial operating mode in the sample analyzer **1** of the present embodiment. The sample analyzer **1** therefore remains in a standby state waiting to receive a measurement start instruction. The microcomputer **6** displays a screen on the liquid crystal display which alerts the operator to the standby state (step S4).

In the standby state, the operator can change the measurement mode by operating the display and operation unit **7**. FIG. **8** is a schematic view of an input screen for setting the measurement mode. This screen is provided with discrete display regions including the sample number **120**, type of sample uptake mode **121**, type of discrete test (measurement mode) **122**, and type of sample **123**. The three sample uptake modes include a manual mode for aspirating a sample after the operator has manually inserted a sample container in the sample aspiration nozzle **18**, a capillary mode for aspirating a measurement sample via the sample aspiration nozzle **18** after the operator has previously prepared the measurement sample by mixing a sample and reagent, and a closed mode for supplying a sample by automatically transporting a sample container using a conveyer device. The types of samples include NORMAL, which are normal blood samples; HPC, which are hematopoietic progenitor cell samples; and BODY FLUID, which are other fluids of the body. The operator can specify the sample take-up mode, measurement mode, and type of sample. When the blood measurement mode has been specified, the NORMAL sample type is specified, and an optional sample take-up mode and measurement mode are specified. When specifying the BODY FLUID measurement mode, the operator specifies MANUAL mode as the take-up mode, [CBC+DIFF], [CBC+DIFF+RET], [CBC+DIFF+NRBC], or [CBC+DIFFNRBC+RET] as the DISCRETE test, and [BODY FLUID] as the type of sample. In step S4, the operator specifies the desired mode. The operator presses the start switch to start the measurement when blood measurement is performed without changing the initially set measurement mode(step S5: N). The microcomputer **6** receives the instruction to start the measurement (step S6), and the blood sample is aspirated by the sample aspiration nozzle (step S7).

After the blood sample has been aspirated, the sample is introduced to the previously mentioned sampling valve **18**, and the necessary sample preparation is performed for the measurement according to the type discrete test of the measurement mode (step S14). The measurement operation is then executed for this measurement sample (step S16). When [7] is set as the type of discrete test, for example, HGB, WBC/BASO, DIFF, RET, NRBC, and RBC/PLT measurement samples are prepared. Thereafter, the WBC/BASO, DIFF, RET, and NRBC measurement samples are measured by the white blood cell detection unit **41**, the RBC/PLT measurement sample is measured by the RBC/PLT detection unit **42**, and the HGB measurement sample is measured by the HGB detection unit **43**. At this time, the WBC/BASO, DIFF, RET, and NRBC measurement samples are introduced to the white blood cell detection unit **41** in the order NRBC, WBC/BASO, DIFF, RET and sequentially measured since only a single white blood cell detection unit **41** is provided. In this measurement operation, the calculation unit **62** creates particle distribution maps (scattergram, histogram). The scattergram created from the optical information obtained by the DIFF measurement is described below. The calculation unit **62** generates a two-dimensional scattergram (particle distribution map) using, as characteristic parameters, the side scattered light and side fluorescent light among the photoreception signals output from the white blood cell detection unit **41** in the DIFF measurement. This scattergram (referred to as "DIFF scattergram" hereinafter) plots the side scattered light intensity on the X axis and the side fluorescent light on the Y axis; red blood cell ghost clusters, lymphocyte clusters, monocyte clusters, neutrophil+basophil clusters, and eosinophil clusters normally appear. These clusters are recognized by processing performed on the DIFF scattergram by the data analyzing unit **64**.

Analysis processing is then performed based on the particle distribution maps obtained by the measurement (step S18). In the analysis processing, the data analyzing unit **64** of the microcomputer **6** classifies the four white blood cell clusters (lymphocyte cluster, monocyte cluster, neutrophil+basophil cluster, and eosinophil cluster), and the red blood cell ghost cluster as shown in FIG. **12** from the DIFF scattergram prepared by the calculation unit **62** when the DIFF measurement samples were measured by the white blood cell detection unit **41**. In the analysis process of the present embodiment, each particle plotted on the scattergram and the degree of attribution of particles to each cluster at a distance from the center of gravity of each cluster is obtained. Then, each particle is attributed to a cluster according to the degree of attribution. The particle classification method is disclosed in detail in U.S. Pat. No. 5,555,196. The basophil cluster, and white blood cell clusters other than basophils, and the red blood cell ghost cluster are classified on the scattergram obtained by the WBC/BASO measurement. White blood cells are classified in five groups based on the results of the four classifications and numbers of white blood cells (refer to FIG. **12**) by the analysis processing of the DIFF scattergram, and the results of the two classification and numbers of white blood cells by the analysis processing of the WBC/BASO scattergram. Specifically, the data analysis unit **64** subtracts the basophil cell count obtained by the analyzing the WBC/BASO scattergram from the neutrophil+basophil cell count obtained by analyzing the DIFF scattergram, to obtain the neutrophil cell count and the basophil cell count. Thus, five classifications of white blood cells are obtained as well as the number of blood cells in each classification. In addition, the trough is detected in the curve in the unidimensional histogram created based on the characteristic information from the detection unit **42**, and the particles are classified as red blood cells and platelets in the RBC/PLT measurement. The analysis results thus obtained are output to the display unit **302** of the data processing unit **3** (step S20).

When input specifying the measurement mode is received as described above in step S5, the microcomputer **6** sets the parameters (operating conditions) for the body fluid measurement, for example, the reaction chamber to use and the set time of the measurement and the like (step S8). In the present embodiment, the measurement time is three times the time for blood measurement, as will be described later.

The measuring unit **2** starts the pre sequence (step S10) when the measurement mode has been switched from the previous measurement mode (in this instance, the blood measurement mode) to the body fluid measurement mode (step S9). The pre sequence is a process of preparing for the body fluid measurement. Since samples which have a low concentration of blood cell component are measured in the body fluid measurement, the setting is switched from the

blood measurement mode ([1:NORMAL] is displayed in FIG. **8**) to the body fluid measurement mode, and the lack of background influence is confirmed in the body fluid measurement results.

The pre sequence includes a blank check operation. The blank check determination standard of the pre sequence is set at a fraction and is more strict than the determination standard of the blank check (for example, the blank check performed after power on and automatic wash) performed in the blood measurement mode. When the setting is changed from the body fluid measurement mode to the blood measurement mode, this pre sequence is not performed since there is no background influence (carry over effect) on the normal blood measurement results. Furthermore, when body fluid samples are measured in a repeated body fluid measurement mode, this pre sequence is not performed since there is normally no background influence. There is concern, however, that the next sample measurement may be affected when the body fluid sample analysis results exceed a predetermined value due to an extremely high number of particles in the body fluid since the measurement results are high, and therefore the operator is alerted of this concern that the analysis results of the next sample may be affected. Then, the blank check measurement is performed. A configuration is desirable in which a message "please press VERIFY" is output to the screen, and the blank check is performed when the operator presses the VERIFY button. In this case, a configuration is possible in which a CANCEL button may be provided on the screen to transition to the standby screen without performing a blank check when the operator presses the CANCEL button. It is also desirable that a flag indicate the low reliability of the measurement results when a blank check is not performed. Wasted reagent and time can thus be avoided by performing an additional blank check only when needed.

FIG. **9** is a flow chart showing the sequence of the pre sequence process performed when the measurement mode is changed from the blood measurement mode to the body fluid measurement mode. The sample analyzer **1** performs the pre sequence by measuring a blank sample using the measuring unit **2** (step S**31**), comparing the measurement result with predetermined tolerance values and determining whether or not the measurement results are less than the tolerance values using the microcomputer **6** (step S**32**). When the measurement results are less than the tolerance values, the microcomputer **6** ends the pre sequence and the process returns. When the measurement results are not less than the tolerance value, the microcomputer **6** determines whether or not the blank check was executed the set number of times (for example, three times) (step S**33**), and when the number of executions of the blank check is less than a predetermined number, the process returns to step S**31** and the blank check is performed again for the predetermined number of times. When the measurement results of the blank check performed a predetermined number of times are not less than the tolerance values, a screen is displayed with includes a VERIFY button, BLANK CHECK button, and AUTOMATIC WASH button and the blank check measurement results are displayed on the display and operation unit **7** (step S**34**). When the operator has pressed the VERIFY button (step S**35**), the microcomputer **6** ends the pre sequence and the process returns. When the BLANK CHECK button has been pressed (step S**36**), the process returns to step S**31** and the blank check is performed again; when the AUTOMATIC WASH button has been pressed (step S**37**), automatic washing is performed using a special washing solution (step S**38**), and thereafter the process returns to step S**31** and the blank check is performed again.

When the pre sequence ends as described above, the sample analyzer **1** enters the standby state (step S**11**). When the operator presses the start switch and starts the body fluid measurement, the sample aspiration nozzle **18** of the measuring unit **2** is immersed in the sample container in the same manner as for the manual measurement of the blood sample. When the instruction to start measurement is received by the microcomputer **6** (step S**12**), the body fluid aspiration begins (step S**13**).

After the body fluid sample has been aspirated, the body fluid sample is introduced to the sampling valve **91** in the same manner as the blood sample. Then, the RBC/PLT measurement sample is prepared by the reaction chamber **13** (step S**15**). Subsequently, the DIFF measurement sample is measured by the white blood cell detection unit **41**, and the RBC/PLT measurement sample is measured by the RBC/PLT detection unit **42** (step S**17**). Since only the DIFF measurement sample is measured by the white blood cell detection unit **41** in the body fluid measurement mode, the measurement is completed in a shorter time than the blood measurement even though the measurement time is longer than the measurement time in the blood measurement mode. the analysis accuracy of the low particle concentration body fluid sample can therefore be improved by increasing the measurement time of the body fluid measurement to be longer than the measurement time of the blood measurement. Although the measurement accuracy can be improved due to the increased number of particles counted by lengthening the measurement time, a two to six fold increase in the measurement time is suitable because the sample processing ability is reduced when the measurement time is excessively long, and there is a limit to the performance of the syringe pump which delivers the measurement sample to the white blood cell detection unit **41**. In the present embodiment, the measurement time in the body fluid measurement mode is set at three times the measurement time of the blood measurement mode.

The RBC/PLT measurement sample is introduced to the electrical resistance detection unit **41** in the same manner for all measurement modes, and measurement is performed under a fixed flow speed condition. The analysis processing is performed thereafter based on the characteristic information obtained by the measurements (step S**19**), and the analysis results are output to the display unit **302** of the data processing unit **3** (step S**21**). In the analysis processing of the blood measurement mode, the DIFF scattergram and the like are analyzed, and information is calculated for five types of white blood cell subclasses (NEUT: neutrophil, LYMPH: lymphocyte, MONO: monocyte, EO: eosinophil, and BASO: basophil), whereas in the analysis processing of the body fluid measurement mode, two subclasses (MN: mononuclear cell, PMN: polymorphonuclear cell) are classified in a partially integrated form because there are a lesser number of blood cells and these cells are sometimes damaged. The lymphocytes and monocytes belong to mononuclear cells, and neutrophils, eosinophils, and basophils belong to polymorphonuclear cells. Since the classification algorithm is the same as the algorithm described for the analysis processing in the blood measurement mode, further description is omitted.

Next, the analysis results obtained in step S**19** are compared to the tolerance value (predetermined threshold value) (step S**22**). The tolerance value is the same value as the tolerance value used in the blank check of the pre sequence

performed in step S10. When the analysis result is greater than the tolerance value (step S22: Y), the verification screen **151** at the start of the blank check is displayed, as shown in FIG. **17**. A message is displayed on the verification screen **151** indicating there is concern that the measurement of the next sample may be influenced due to the high measurement result. Then, the blank check measurement is performed. A message display area **152** for displaying the message "please press the VERIFY button", a VERIFY button **153**, and a CANCEL button **154** are displayed. Next, determinations are made as to whether or not the user has pressed the VERIFY button **153** or the CANCEL button **154** (step S24), and the blank check is executed when the VERIFY button has been pressed (VERIFY in step S24) (step S25). The process returns to step S5 without performing the blank check when the analysis result obtained in step S19 is less than the tolerance value (step S22: N), and the when the CANCEL button has been pressed (CANCEL in step S24).

Anomalous particles (macrophages, mesothelial cells, tumor cells and the like) other than blood cells may be present in the body fluid sample. Although it is rare for such anomalous cells to be present in cerebrospinal fluid, such cells appear comparatively frequently in abdominal and thoracic fluids. The influence of these anomalous particles must be eliminated in order to obtain a high precision classification of blood cells within the body fluid regardless of the type of body fluid. White blood cells in body fluid can be measured with greater precision based on the new knowledge than anomalous particles appear in the top part of the DIFF scattergram produced by this blood cell analyzer of the present invention. This aspect was not considered in the previously mentioned conventional art.

FIG. **10** is a schematic view of a scattergram obtained by measuring and analyzing a DIFF measurement sample prepared from body fluid and white blood cell measurement reagent in the body fluid measurement mode of the blood cell analyzer **1** of the present embodiment. The vertical axis of the scattergram represents the side fluorescent light intensity (the fluorescent light intensity at the top is greatest), and the horizontal axis represents the side scattered light intensity (the scattered light intensity at the right side is greatest). A red blood cell ghost Gc caused by hemolysis is distributed in the region LF in which the fluorescent light intensity is weakest in the scattergram, anomalous particles such as mesothelial cells and the like is distributed in the region HF in which the fluorescent light intensity is greatest, and mononuclear white blood cells Mc and polynuclear white blood cells Pc are distributed in the intermediate region MF. In the analysis of the scattergram, the particle component distributed in the region MF is analyzed as white blood cells after excluding region LF and region HF, and the particles are classified and counted in two groups. Lymphocytes and monocytes are included in the mononuclear white blood cells Mc, and neutrophils, basophils, and eosinophils are included in the polynuclear white blood cells Pc.

Since fewer and damaged blood cells are contained in body fluid, white blood cells are classified and counted as mononuclear white blood cells and polynuclear white blood cells when analyzing white blood cells in body fluid.

Anomalous particles (nucleated cells such as tumor cells, macrophages, mesothelial cells) other than blood cells may also be present in body fluid. Although it is rare for such anomalous cells to be present in cerebrospinal fluid, such cells appear comparatively frequently in abdominal and thoracic fluids. In the scattergram of FIG. **10**, such nucleated cells other than white blood cells are distributed in region HF. In the present embodiment, it is possible to determine accurate white blood cells counts even in body fluid which contains such nucleated cells other than white blood cells since nucleated cells other than white blood cells can be identified. The degree of occurrence of anomalous cells can be determined by counting the cells which appear in region HF. In the present embodiment, cells are demarcated in the regions LF, MF, and HF by threshold values for demarcating each region; these threshold values may also be changed manually.

FIG. **11** compares the analysis results of the blood cell analyzer **1** of the present embodiment and the count results of a reference method to show the validity of the scattergram analysis method described above. The sample material is thoracic fluid; in the drawing, "this method" refers to the white blood cell count (WBC) and anomalous particle count (Others) calculated by the blood cell analyzer **1** of the present embodiment, and "Ref" refers to the calculation result by the reference methods (Fuchs Rosenthal calculation method and site-spin method). Examples 1, 2, and 3 are the results of analysis of thoracic fluid in which anomalous particles were plentiful, and the correlation between the reference methods and the analysis results of the blood cell analyzer **1** of the present invention can be readily understood.

FIG. **13** shows a screen **200** which is displayed on the display unit **302** of the data processing unit **3**, showing the analysis results of the DIFF measurement sample prepared from blood. A sample number display region which displays a sample number **101** is provided at the top of the screen **200**, and an attribute display region which displays patient attributes is provided adjacently. The attribute display region specifically includes a patient ID, patient name, date of birth, sex, hospital department/ward, attending physician, date of measurement, time of measurement, comments and the like. A measurement result display region which displays the measurement results is provided at the bottom of the attribute display region. The measurement result display region includes several pages, and these pages can be displayed by selecting a plurality of tabs **102**. Tabs have a plurality of arrangements matching the main screen, graph screen, and measurement items. FIG. **12** is a screen which is displayed when the graph screen tab has been selected. A graph display region **104** for displaying graphs and a measurement value display region **103** for displaying the measurement result values are provided in the left half of the measurement value display region, and a distribution map display region for displaying the measurement result distribution map **105** is provided in the right half. WBC, RBC, . . . , NEUT#, . . . , BASO#, . . . , NEUT#, . . . , BASO % and the like, data, and units are displayed in the measurement value display region, and flagging results representing sample anomalies and disease suspicions which are clinically useful information relating to WBC, PLT, RBC or RET are displayed in the flag display region **104**.

Six distribution maps are displayed in the distribution map display region **105**. The scattergram on the upper left side is a DIFF scattergram. The WBC/BASO scattergram is shown at the top right, the immature cell (IMI) scattergram is shown at mid left, and the RET scattergram is shown at mid right. The RBC scattergram is shown at the bottom left, and the ELT scattergram is shown at the bottom right.

FIG. **14** shows a screen **110** displayed in the display area **302** of the data processing unit **3** as the measurement results of the DIFF measurement sample prepared from body fluid. A sample number display region **111** for displaying a sample number is provided at the top of the screen **110**, and a patient attribute display region is provided adjacently. An [F], which

indicates measurement has been conducted in the body fluid measurement mode, is displayed at the left end of the sample number display region **111**. Thus, it can be clearly recognized that the analysis results are for body fluid measurement results. The measurement result display region includes a plurality of pages which are selectable by tab **112**. In this example, the tab for body fluid measurement is selected.

The measurement value display region **113** includes the name of the measurement items for body fluid measurement rather than the measurement results of the blood measurement mode; WBC-BF (WBC count), RBC-BF (RBC count), MN# (mononuclear cell count (lymphocytes+monocytes)), PMN# (polymorphonuclear cell count (neutrophils+basophils+eosinophils)), MN % (ratio of mononuclear cells among white blood cells), PMN % (ratio of polymorphonuclear cells among white blood cells), measurement values, and units are associated and displayed. A flag display region **114** is provided in the body fluid measurement similar to the blood measurement. Two distribution maps **115** are displayed in the distribution map display region, and the top scattergram is a DIFF scattergram. The bottom scattergram is an RBC scattergram.

FIG. **15** shows an example in which the Research BF tab **112** is selected in the screen **110** of FIG. **14**. This screen displays the same items as screen **110** with the exception that a research parameter display region **116** is also displayed. The research parameter display region **116** displays number of particles in region HF [HF-BF#], the ratio of the number of particles in the region HF relative to the number of particles in the region including both region HF and region MF [HF-BF %], and the number of particles in the region including both region HF and region MF [TC-BF#] in FIG. **10**. [HF-BF %] is the percentage of HF-BF relative to TC-BF.

FIG. **16** shows a screen **120** showing a list of stored samples which is displayed on the display unit **302** of the data processing unit **3**. Reference number **130** refers to a patient attribute display region. Provided above this region is a measurement result display region which displays the measurement result selected by a tab. A row **131** on the left end of the measurement result display region is used to indicate whether the validation operation has been performed or not for the measurement result. A "V" symbol indicates validation has been performed. A row **132** on the right indicates the measurement mode. An "F" symbol indicates the measurement results are for the body fluid mode. Although there are high value samples that require blank checking in the body fluid mode, and inverted "F" symbol can be displayed to indicate the blank check has not been performed (that is, CANCEL was selected in step S**24**).

Although the structure and functions of the blood cell analyzer of the present invention have been described as being pre-established in the blood cell analyzer, the same functions may be realized by a computer program so that the functions of the present invention can be realized in a conventional blood cell analyzer by installing the computer program in a conventional blood cell analyzer.

Although the amount of sample, type of reagent, and amount of reagent are the same when preparing measurement samples for the white blood cell classification measurement in the blood measurement mode and the white blood cell classification measurement in the body fluid measurement mode in the present embodiment, the present invention is not limited to this configuration inasmuch as the amount of sample and the amount of reagent used to prepare a measurement sample for white blood cell classification in the body fluid measurement mode may be greater than the amount of sample and the amount of reagent used to prepare a measurement sample for white blood cell classification in the blood measurement mode. Since the measurement time is greater and the amount of measurement sample needed for measurement is greater for white blood cell classification in the body fluid measurement mode than in the blood measurement mode, it is thereby possible to prepare suitable amounts of measurement sample for white blood cell classification in the blood measurement mode and for white blood cell classification in the body fluid measurement mode. Moreover, the type of reagent used for white blood cell classification in the blood measurement mode may differ from the type of reagent used for white blood cell classification in the body fluid measurement mode.

Although white blood cell classification is performed in the body fluid measurement mode using scattered light and fluorescent light in the present embodiment, the present invention is not limited to this configuration inasmuch as white blood cell classification may also be performed in the body fluid measurement mode using, for example, scattered light and absorbed light. The measurement of absorbed light may be accomplished by preparing a measurement sample by mixing a staining reagent to stain the white blood cells, and other reagent together with the sample, supplying this measurement sample to a flow cell to form a sample flow within the flow cell, irradiating this sample flow with light, and receiving the light emitted from the sample flow via a photoreceptor element such as a photodiode or the like. The light is absorbed by the white blood cells when the white blood cells pass through the flow cell, and the degree of that absorption can be grasped as the amount of light received by the photoreceptor element. Such measurement of absorbed light is disclosed in U.S. Pat. Nos. 5,122,453, and 5,138,181. furthermore, electrical resistance may be measured rather than scattered light, in which case white blood cells can be classified by the electrical resistance and absorbed light.

The invention claimed is:

**1**. A sample analyzer comprising:

a plurality of detectors each configured to sense cells in a sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring cells in the body fluid sample, and wherein a respective sequence of operations for measuring cells in the blood sample and in the body fluid sample comprises (a) a sensing operation comprising operations of preparing for measurement and operating a detector to sense cells in the sample and (b) an analyzing operation comprising operations of analyzing sample measurements from the sensing operation and displaying analysis results, the sensing operation performed in the body fluid measuring mode being different, at least partially, from the sensing operation performed in the blood measuring mode, and further wherein the plurality of detectors

include one or more multi-mode detectors configured to operate in both the blood measuring mode and the body fluid measuring mode,

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise concurrent display of a blood sample option and a body fluid sample option each independently selectable from the other on the input screen and (2) one or more test modes displayed separately from a selected one of the at least two sample-type options, wherein selecting the body fluid sample option from the at least two sample-type options and setting a test mode from the one or more test modes is based on repective discrete user inputs separately received in the input screen;

in response to (I) a user input, on the input screen, of selecting the blood sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting one test mode from the displayed one or more test modes, perform the sensing operation in the blood measuring mode to: prepare a blood measurement sample from the blood sample; introduce at least part of the prepared blood measurement sample into a multi-mode detector; and operate said multi-mode detector to sense cells in the introduced blood measurement sample, and further perform the analyzing operation in the blood measuring mode to: analyze blood-sample measurements of cells sensed in the introduced blood measurement sample; and display analysis results of the blood-sample measurements on a first test result screen; and

in response to (I) a user input, on the input screen, of selecting the body fluid sample option from the displayed at least two test-sample options and (II) an additional user input, on the input screen, of setting said one or a different test mode from the displayed one or more test modes, perform the sensing operation in the body fluid measuring mode to: prepare a body fluid measurement sample from the body fluid sample; introduce at least part of the prepared body fluid measurement sample into said multi-mode detector; and operate said multi-mode detector to sense cells in the introduced body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze body-fluid-sample measurements of the cells sensed in the introduced body fluid measurement sample; and display analysis results of the body-fluid-sample measurements on a second test result screen.

**2**. The sample analyzer according to claim **1**, wherein the sensing operation performed in the blood measuring mode comprises an operation of sensing the cells in the introduced blood measurement sample for a first measurement time, and

the sensing operation performed in the body fluid measuring mode comprises an operation of sensing the cells in the introduced body fluid measurement sample for a second measurement time, wherein the second measurement time is longer than the first measurement time according to a cell concentration of the sample.

**3**. The sample analyzer according to claim **2**, wherein a ratio between the first and second measurement times falls within a predetermined range.

**4**. The sample analyzer according to claim **1**, wherein the prepared blood measurement sample and the prepared body fluid measurement sample contain blood and body fluid, respectively, in an equal amount.

**5**. The sample analyzer according to claim **1**, wherein the prepared blood measurement sample and the prepared body fluid measurement sample contain a reagent in an equal amount.

**6**. The sample analyzer according to claim **1**, further comprising a conveyor device, wherein the sensing operation performed in the body fluid measuring mode comprises automatically transporting a sample container to a position for aspiration of the body fluid sample from the sample container.

**7**. A sample analyzer comprising:

a plurality of detectors comprising at least one optical detector for optically sensing cells in a sample and at least one electrical detector for electrically sensing cells in the sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring cells in the body fluid sample, and wherein a respective sequence of operations for measuring cells in the blood sample and in the body fluid sample comprises (a) a sensing operation comprising operations of preparing for measurement and operating a detecter to sense cells in the sample and (b) an analyzing operation comprising operations of analyzing measurements from the sensing operation and displaying analysis results, and further wherein the plurality of detectors include one or more multi-mode detectors configured to operate in both the blood measuring mode and the body fluid measuring mode,

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise concurrent display of a blood sample option and a body fluid sample option each independently selectable from the other on the input screen and (2) one or more test modes displayed separately from a selected one of the at least two sample-type options;

in response to (I) a user input, on the input screen, of selecting the blood sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting one test mode from the displayed one or more test modes, perform the sensing operation in the blood measuring mode to: prepare a blood measurement sample from the blood sample; introduce at least part of the prepared blood measurement sample into an optical detector; and operate the optical detector to optically sense white blood cells in the introduced blood measurement sample, and further perform the analyzing operation in the blood measuring mode to: analyze blood-sample measurements of the white blood cells sensed in the introduced blood measurement sample; count each of five types of white blood

cells based on the analyzed blood-sample measurements; and display a count of each of the five types of white blood cells; and

in response to (I) a user input, on the input screen, of selecting the body fluid sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting said one or a different test mode from the displayed one or more test modes, perform the sensing operation in the body fluid measuring mode to: prepare a body fluid measurement sample from the body fluid sample; introduce at least part of the prepared body fluid measurement sample into an electrical detector; operate said electrical detector to electrically sense cells in the introduced body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze body-fluid-sample measurements of cells sensed in the introduced body fluid measurement sample; count mono-nucleated cells and poly-nucleated cells based on the analyzed body-fluid-sample measurements; and separately display in a screen a count of the mono-nucleated cells and a count of the poly-nucleated cells.

**8**. The sample analyzer according to claim **7**, wherein the analyzing operation performed in the blood measuring mode comprises operations to obtain a total count of the white blood cells sensed in the introduced blood measurement sample and display the total count of the white blood cells, and the analyzing operation performed in the body fluid measuring mode comprises operations to obtain a total count of nucleated cells sensed in the introduced body fluid measurement sample and display the total count of the nucleated cells.

**9**. The sample analyzer according to claim **8**, wherein the analyzing operation performed in the blood measuring mode comprises displaying a first test result screen for displaying test results obtained in the blood measuring mode, and the analyzing operation performed in the body fluid measuring mode comprises displaying a second test result screen for displaying test results obtained in the body fluid measuring mode.

**10**. The sample analyzer according to claim **9**, wherein the first test result screen comprises first and second separate screen regions for displaying test results, wherein the first screen region is configured to display the total count of the white blood cells sensed in the introduced blood measurement sample, and the second screen region is configured to display the count of each of the five types of the white blood cells.

**11**. The sample analyzer according to claim **10**, wherein the second test result screen comprises third screen region for displaying test results, wherein the third screen region is configured to separately display the count of the mono-nucleated cells and the count of the poly-nucleated cells.

**12**. The sample analyzer according to claim **11**, wherein the analyzing operation performed in the body fluid measuring mode comprises calculating a relative cell amount of the mono-nucleated cells and a relative cell amount of poly-nucleated cells sensed in the introduced body fluid measurement sample, and

the third screen region is configured to separately display the relative cell amount of the mono-nucleated cells and the relative cell amount of the poly-nucleated cell.

**13**. The sample analyzer according to claim **11**, wherein the second test result screen comprises a fourth screen region separate from the third screen region, wherein the fourth screen region is configured to display the total count of the nucleated cells.

**14**. The sample analyzer according to claim **13**, wherein the second test result screen comprises a fifth screen region separate from the third and fourth screen regions, the fifth screen region being configured to display a flagging result representing a disease suspicion.

**15**. The sample analyzer according to claim **7**, wherein the analyzing operation performed in the body fluid measuring mode comprises removing a red blood cell ghost from the body-fluid-sample measurements.

**16**. A sample analyzer comprising:

a plurality of detectors each configured to sense cells in a sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring cells in the body fluid sample, and wherein a respective sequence of operations for measuring cells in the blood sample and in the body fluid sample comprises a sensing operation comprising operations of preparing for measurement and operating a detector to sense cells in the sample, and further wherein the plurality of detectors include one or more multi-mode detectors configured to operate in both the blood measuring mode and the body fluid measuring mode,

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise concurrent display of a blood sample option and a body fluid sample option each independently selectable from the other on the input screen, and (2) one or more test modes displayed separately from a selected one of the at least two sample type options, wherein selecting the body fluid sample option from the at least two sample-type options and setting a test mode from the one or more test modes is based on respective discrete user inputs separately received in the input screen;

in response to (I) a user input, on the input screen, of selecting the blood sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting one test mode from the displayed one or more test modes, perform the sensing operation in the blood measuring mode to: prepare a blood measurement sample from the blood sample; introduce at least part of the prepared blood measurement sample into a multi-mode detector; and operate said multi-mode detector to sense cells in the introduced blood measurement sample; and

in response to (I) a user input, of selecting the body fluid sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting said one or a different test mode from the displayed one or more test modes, perform the sensing operation in the body fluid measuring mode to: prepare a body fluid measure-

ment sample from the body fluid sample; introduce at least part of the prepared body fluid measurement sample into said multi-mode detector; and operate said multi-mode detector to sense cells in the introduced body fluid measurement sample,

wherein the sensing operation performed in the body fluid measuring mode comprises an operation of pre-washing said multi-mode detector to reduce a carryover effect on measurements of the body fluid measurement sample, wherein the controller is programmed to automatically initiate said pre-washing, during said sensing operation in the body fluid measuring mode before introduction of the body fluid measurement sample into said multi-mode detector, and the controller is programmed not to introduce the prepared body fluid measurement sample into said multi-mode detector before said pre-washing is completed.

**17**. The sample analyzer according to claim **16**, wherein said pre-washing is automatically initiated in the sensing operation in the body fluid measuring mode but not automatically initiated in the sensing operation in the blood measuring mode.

**18**. The sample analyzer according to claim **16**, wherein said pre-washing includes using a solution specifically prepared for said pre-washing.

**19**. The sample analyzer according to claim **16**, wherein the controller is programmed to perform a blank check in which the controller:

introduces a cell-free sample into said multi-mode detector, the cell-free sample having no cells contained in the cell-free sample;

senses the cell-free sample by said multi-mode detector; and

analyzes measurements of the cell-free sample and count cells carried over into the cell-free sample from a test sample previously measured.

**20**. The sample analyzer according to claim **19**, wherein the controller is programmed to perform the blank check automatically without a manual operation by a user to initiate the blank check.

**21**. The sample analyzer according to claim **16**, wherein said pre-washing includes more than one washing of said multi-mode detector during the same sensing operation in the body fluid measuring mode.

**22**. The sample analyzer according to claim **21**, further comprising a post-detection chamber communicating with said multi-mode detector, wherein the post-detection chamber is located above said multi-mode detector and configured to receive and temporary store the measurement sample, which is already sensed by said multi-mode detector, for adjustment of pressure at said multi-mode detector, and further wherein the post-detection chamber automatically receives, more than once at a time interval, a solution used in said pre-washing during the same sensing operation in the body fluid measuring mode.

**23**. The sample analyzer according to claim **16**, further comprising a conveyor device, wherein the sensing operation performed in the body fluid measuring mode comprises automatically transporting a sample container to a position for aspiration of the body fluid sample from the sample container.

**24**. A sample analyzer comprising:

a plurality of detectors each configured to sense cells in a sample, the sample selectively comprising (i) a blood sample or (ii) a body fluid sample, wherein the body fluid sample contains body fluid, other than blood, which is selected from a group consisting of cerebrospinal fluid, thoracic fluid, abdominal fluid, fluid collected in a cardiac sac, synovial fluid, dialysate from peritoneal dialysis, and intraperitoneal rinse;

a controller programmed to selectively operate the sample analyzer in a blood measuring mode or a body fluid measuring mode, wherein the blood measuring mode includes a sequence of operations for measuring cells in the blood sample, and the body fluid measuring mode includes a sequence of operations for measuring blood cells in the body fluid sample, and wherein a respective sequence of operations for measuring blood cells in the blood sample and in the body fluid sample comprises (a) a sensing operation comprising operations of preparing for measurement and operating a detector to sense cells in the sample, and (b) an analyzing operation comprising operations of analyzing sample measurements from the sensing operation and displaying analysis results, and further wherein the plurality of detectors include one or more multi-mode detectors configured to operate in both the blood measuring mode and the body fluid measuring mode,

the controller programmed to:

display on an input screen (1) at least two sample-type options that comprise concurrent display of a blood sample option and a body fluid sample option each selectable independently from the other on the input screen and (2) one or more test modes displayed separately from a selected one of the at least two sample-type options,

in response to (I) a user input, on the input screen, of selecting the body fluid sample option from the displayed at least two sample-type options and (II) an additional user input, on the input screen, of setting one test mode from the displayed one or more test modes,

(A) perform the sensing operation in the body fluid measuring mode to: prepare a first body fluid measurement sample from the body fluid sample; and sense cells in the first body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze first measurements of the cells sensed in the first body fluid measurement sample and count red blood cells based on the analyzed first measurements, and

(B) perform the sensing operation in the body fluid measuring mode to: prepare a second body fluid measurement sample from the body fluid sample; and sense cells in the second body fluid measurement sample, and further perform the analyzing operation in the body fluid measuring mode to: analyze second measurements of the cells sensed in the second body fluid measurement sample; and count mono-nucleated cells and poly-nucleated cells based on the analyzed second measurements, wherein the controller is programmed to separately display in a screen a count of the red blood cells, a count of the mono-nucleated cells and a count of the poly-nucleated cells.

**25**. The sample analyzer according to claim **24**, wherein the analyzing operation performed in the blood measuring mode comprises displaying a first test result screen for displaying test results obtained in the blood measuring mode, and the analyzing operation performed in the body fluid measuring mode comprises displaying a second test result screen for displaying test results obtained in the body fluid measuring mode, and

wherein the second test result screen comprises first and second separate screen regions for displaying test results, wherein the first screen region is configured to display a total count of nucleated cells sensed in the second body fluid measurement sample, and the second screen region is configured to separately display the count of the mono-nucleated cells and the count of the poly-nucleated cells sensed in the second body fluid measurement sample.

**26**. The sample analyzer according to claim **25**, wherein the analyzing operation performed in the body fluid measuring mode comprises calculating a relative cell amount of the mono-nucleated cells and a relative cell amount of the poly-nucleated cells in the second body fluid measurement sample, and the second screen region is configured to separately display the relative cell amount of the mono-nucleated cells and the relative cell amount of the poly-nucleated cells.



**27**. The sample analyzer according to claim **26**, wherein the second test result screen comprises a third screen region separate from the first and second screen regions, the third screen region being configured to display a flagging result representing a disease suspicion.

**28**. The sample analyzer according to claim **24**, wherein the analyzing operation performed in the body fluid measuring mode comprises removing a red blood cell ghost from the second measurements by application of a threshold to the second measurements.

**29**. The sample analyzer according to claim **1**, wherein the controller is programmed to remain in the body fluid measuring mode after completing the sequence of operations in the body fluid measuring mode for measuring cells in a body fluid sample until the body fluid measuring mode is manually switched to the blood measuring mode.

* * * * *

## CERTIFICATE OF SERVICE

I hereby certify that on this 26th day of September, 2022, I caused the foregoing brief to be electronically filed using the CM/ECF system, which will send notification of such filing to all parties of record.

I further certify that pursuant to Fed. R. App. P. 25(c)(3), I shall cause six paper copies of the foregoing brief to be filed at the address provided below within five business days after the court's issuance of a notice requesting paper copies:

Clerk of Court
United States Court of Appeals for the Federal Circuit
717 Madison Place, N.W.
Washington, D.C. 20439

September 26, 2022

*/s/ James R. Sobieraj*
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## CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a) because it contains 11,223 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f) and Federal Circuit Rules 28(a)(2) and 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word in Times New Roman 14 point font.

September 26, 2022

Respectfully Submitted,

*/s/ James R. Sobieraj*

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